REMARKS/ARGUMENTS

Claims 9-13 are pending. Reconsideration is respectfully requested.

The present invention relates to a method of treating impaired gastric accommodation.

Obviousness-type Double Patenting

Claims 9-13 stand rejected based on obviousness-type double patenting in view of Claims 11 and 12 of Nagasawa et al, U. S. Patent 5,981,557. This ground of rejection is respectfully traversed.

The Examiner continues to assert that the method of utility described in Claims 11 and 12 of the '557 patent is the same as the method claimed in the present invention. Stated simply, the gastrointestinal condition known as digestive dysmotility is the specific disorder treated by the method of the patent. The disorder treated in the present invention is an entirely different disorder involving a different component of the gastrointestinal system which is the fundus of the stomach. The method of present claims 9-13 does, in fact, represent a different utility than the method of treatment of Claims 11 and 12 of the '557 patent.

In considering this ground of rejection, applicants again refer to the earlier presentation or discussion of the international gastroenterological conferences held in Rome. Early on, in Rome 1, functional dyspepsia was defined into four subgroups which are (1) dysmotility-type dyspepsia, (2) ulcer-like dyspepsia, (3) reflux dyspepsia and (5) non-specific dyspepsia. Thus, early on, motility disorders of the gastrointestinal tract have been recognized, and it is this method that is claimed in the '557 patent. (Again, note that the discussion of the background of the invention on page 1 of the present specification mentions the recognition of motility disfunction of the gastrointestinal tract.) At the time of the invention discussed in the '557 patent, impairment of the gastric fundus of the stomach had not been recognized as a mode of functional disorder of the gastrointestinal system. The

present invention is based on the recognition of this disorder of the upper stomach and that it can be effectively treated by the compound set forth in present Claims 9 and 13.

At this point applicants refer to the attached documents that are identified as A1 to A6. These papers disclose that impaired gastric accommodation occurs not only in patients suffering from functional dyspepsia (FD), but also in patients having certain types of diabetes (see publication B1 attached). Furthermore, impaired gastric accommodation is believed to occur in organic disease patients, depressed patients, and the like, as well as in cases where gastric accommodation occurs in patients being treated with anticancer substances.

In FD patients, symptoms of impaired gastric accommodation can be distinguished from other symptoms according to the criteria established at Rome III, which is the diagnostic criteria of FD. In addition, some people have symptoms of impaired gastric accommodation despite the fact that they do not meet the Rome III criteria. Thus, patients with impaired gastric accommodation can be distinguished from FD patients. Since the compound employed in the present method exhibits the action of relaxing the gastric fundus, the claimed compound can treat impaired gastric accommodation when that accompany various other disorders. On the other hand, Claims 11 and 12 of the '557 patent are directed to a method of treating digestive dysmotility. Accordingly, Nagasawa et al does not suggest the method of the present invention. Withdrawal of the rejection is respectfully requested.

Rejection, 35 U.S.C. §102

Claims 9-13 stand rejected under 35 U.S.C. 102(a) as anticipated by Sorbera et al. This ground of rejection is respectfully traversed.

Applicants maintain their position that the filing of a certified copy of the original Japanese priority application and the filing of a certified English translation of the priority

document perfects the filing date of April 8, 2002 of the priority application of the present U. S. application.

The Examiner has replied by stating on the record at page 7 of the Office Action that the disclosure of the certified translation of the priority case *fails to provide adequate support or enablement in the manner required by the first paragraph* of the first paragraph of 35 USC 112. Absolutely, not one reason is presented *as to why* the specification is not enabling of the present invention. To the contrary, the English translation is the basis for a large portion of the text of the present U. S. application. Thus, the certified translation contains:

(1) A complete description of the background of the invention starting with a discussion of motility disorders of the gastrointestinal tract and progressing through a discussion of conventional therapeutic agents that have been used to treat the disorders up to the point of recognition by those of skill in the art that it is necessary to provide a means of relaxation of the gastric fundus in order to alleviate the discomforting feelings of early satiation and bloating.

(2) An express statement that the discovery of the invention is the alleviation of gastric accommodation by relaxation of the fundus with the compound shown on page 3 of the text.

(3) A generic description of the active compound of the invention.

(4) A description of subgenric aspects of the compound that is used and a complete identification of a number of specific compound embodiments of the active compound.

(5) A specification that an active therapeutic formulation is prepared from a desired compound embodiment for oral or parenteral administration, as well as a thorough description of excipients that are combined with a compound embodiment.

(6) A sufficient description of dosage information.

(7) A very thorough description of several examples of test compounds used to treat impaired gastric accommodation which includes a complete description of barostat tests in dogs and humans.

Clearly, the English translation of the priority document is fully enabling of the present invention. Since that is the case, the foreign priority date of the present application is perfected, and since the perfected priority date is established, the rejection of the claims in view of the Sorbera et al patent is obviated. Withdrawal of the rejection is respectfully requested.

Prior Art Rejection, 35 USC 102

Claims 9-13 stand rejected based on 35 USC 102 as anticipated by each of Nagasawa et al., U.S. Patent No. 5,981,557, Nagasawa et al, JP10-212271 (abstract) and Nakajima et al., J. Smooth Muscle Res. 36:69. This ground of rejection is respectfully traversed.

The Examiner states on pages 9 and 10 of the Office Action that the utility of the present invention is the same as that disclosed in the three cited references. Applicants manifestly disagree. The '557 patent discloses that an aminothiazole compound of the formula shown in column 1 is useful in the treatment of gastrointestinal dysmotility. The '271 reference teaches that a similar aminothiazole compound is useful in the treatment of gastrointestinal tract motion disorders such as complaints of the upper abdomen. The Nakajima et al publication describes that an aminothiazole compound is useful in the treatment of gastrointestinal prokinetic action. However, the disorder which is treated in the present invention is the impairment of gastric accommodation which occurs at the site of the fundus of the stomach. This disorder is not related to the states of gastrointestinal disorder mentioned in the three cited references. In fact, as mentioned above, in the time frame of the discoveries of the three cited references, the impairment of gastric accommodation of the

fundus as a cause of discomforting gastrointestinal effects was not known. Again, this development has been traced in the three Rome documents that have been submitted earlier in the prosecution of the application. Since the three cited documents do not teach the disorder upon which the present claims is based, the language of the present claims in specifying a method of treating impaired gastric accommodation in the preamble and stating in the body of the claim that the treatment is specifically for a human in need of the treatment distinguishes the presently claimed invention over the cited prior art. The Jansen v. Rexall Sundown Inc decision that has been discussed in the case is consistent with applicants' position concerning the patentability of the present invention. Withdrawal of the rejection is respectfully requested.

Claim Rejection, 35 USC 103

Claims 9-13 stand rejected under 35 U.S.C. 103(a) as obvious over of Nagasawa et al., U.S. Patent No. 5,981,557 and Nagasawa et al, JP10-212271 (abstract). This ground of rejection is respectfully traversed.

Applicants continue to traverse the obviousness ground of rejection for the reasons stated previously. The present claims make it clear that to treat impaired gastric accommodation, the active compound of the claims is administered to a human subject in need of treatment by the drug. On the other hand, the two references disclose a method of treating digestive dysmotility, and nothing about treating impaired gastric accommodation which was not recognized as a gastric disorder at the time of the invention of Nagasawa et al.

The '557 patent discloses that an aminothiazole compound having the formula shown in column 1 is useful in the treatment of gastrointestinal dysmotility. The '271 patent discloses that a similar aminothiazole compound is useful in the treatment of gastrointestinal motion disorders such as in complaints of discomfort in the upper abdomen. On the other

hand, the disorder treated in the present invention is impaired gastric accommodation which is distinct from the disorders treated in the cited references.

Drugs which exhibit the effect of improving gastrointestinal tract motility have been reported as is evident from the prior art mentioned in the present specification and papers A1 to A6 mentioned above. However, no drug, except cisapride, exhibit both the effects of relaxing the gastric fundus and of improving gastrointestinal tract motility. Cisapride shows clear effects on motility of the gastric antrum in humans and dogs (see references C1 to C3). Cisapride is used as a gastrointestinal prokinetic drug to enhance gastric emptying (see reference C4). This reference suggests that the drug also has a relaxing the gastric fundus. However, cisapride was withdrawn from the in 2000 because it was found to exhibit adverse effects. Itopride, as a therapeutic agent, has demonstrated as a result of Phase III clinical testing that it is not effective in the treatment of FD, and was withdrawn. Moreover, itopride has never been developed as a drug for the treatment of impaired gastric accommodation.

In view of the comments above, it would not have been obvious to one of skill that the compound which is useful in improving gastrointestinal tract motility would also have an effect of relaxation of the gastric fundus. Moreover, one of skill in the art would not be motivated by the disclosures of the cited references to examine the effect of the claimed compound specifically on the gastric fundus. Accordingly, withdrawal of the outstanding ground of rejection is respectfully requested.

In view of the amendments and remarks above, the application is in condition for allowance. An early notification to such effect is respectfully requested.

Respectfully submitted,

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MAIER & NEUSTADT, P.C.
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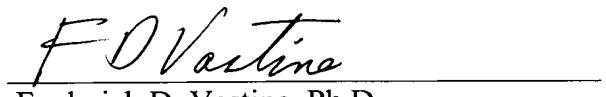

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Alimentary Tract

Effect of the 5-HT3 receptor antagonist, ondansetron, on gastric size in dyspeptic patients with impaired gastric accommodation

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Abstract

Background. A reduction of gastric accommodation after a meal has been documented in patients with idiopathic dyspepsia. In these patients the administration of a 5-HT3 receptor antagonist may reduce some of the dyspeptic symptoms; it is not clear however, whether these drugs influence gastric adaptation to distension as well.

Aim. To evaluate the effects of the 5-HT3 receptor antagonist, ondansetron, on gastric distension after a liquid meal in dyspeptic patients with reduced gastric accommodation.

Methods. Before and after a 500 ml water load, gastric accommodation (area of the proximal and distal stomach) was evaluated using real-time ultrasonography in 21 idiopathic dyspepsia patients and 26 healthy controls. In dyspeptic patients, the test was repeated twice: after the administration of placebo and after ondansetron 8 mg i.v. (in both cases, 15 min prior to the water load). Secondary outcomes were epigastric pain, fullness and nausea as assessed by a visual analogue scale at basal and after ondansetron.

Results. Fasting gastric size was similar in dyspeptic and controls. Compared with controls, dyspeptic patients showed a statistically significant smaller area of the proximal stomach ($14.7 \pm 1.2\,cm^2$ vs. $18.6 \pm 1.4\,cm^2$, respectively; $p = 0.0247$). In dyspeptic patients, gastric proximal and distal size did not change significantly following placebo, whereas after the administration of ondansetron the mean area of the proximal and distal stomach significantly increased (proximal stomach: $14.6 \pm 1.6\,cm^2$ placebo, $20.4 \pm 1.9\,cm^2$ ondansetron, $p = 0.0095$; distal stomach: 8.9 ± 0.9 placebo, $11.4 \pm 1.2\,cm^2$ ondansetron, $p = 0.0409$). Of the symptoms, only nausea was significantly reduced after ondansetron.

Conclusion. In dyspeptic patients with impaired gastric accommodation, ondansetron reverts gastric accommodation to within the range of controls.

Keywords: Functional dyspepsia; Gastric accommodation; 5-HT3 receptor antagonist; Ondansetron; Real-time ultrasonography

1. Introduction

Gastric accommodation is a vagally mediated reflex that occurs after food ingestion and allows the stomach to accommodate the volume of a meal without increasing intra-gastric pressure [1]. The accommodation response to a meal allows the ingestion of large volumes of food and drink without producing symptoms in healthy subjects. In dyspeptic patients symptoms such as nausea, bloating, pain and vomiting are thought to be due to an advanced stimulation of visceral afferent because of increased tension of the stomach wall and impaired accommodation [2] or alteration of cerebral perception with the development of gastric hypersensitivity [3]. While the proof that visceral hypersensitivity present in dyspeptic patients has been shown in a limited group of patients [4], an impaired fundic accommodation with reduced gastric volume has been shown in about 40% of patients with functional dyspepsia in several studies that used different investigational techniques [5–7]. It is therefore conceivable to suppose that the correction of the impaired accommodation might reduce some if not all the dyspeptic symptoms in patients with functional dyspepsia. The study of drugs that may influence gastric accommodation has been the subject

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of several recent works. 5-HT receptors are known to regulate intestinal motility and to mediate ascending stimuli from the gut to the brain [8]. Several drugs which antagonize or stimulate 5-HT receptors are used to treat the symptoms that presumably originate from a derangement of the stomach function [9]. 5-HT3 receptors seem to be involved both in the transmission of the sensation that arises from the stomach and in the process of gastric emptying and accommodation [10]. Among the various drugs that are known to act on 5-HT receptors, the 5-HT3 receptor antagonists (alosetron, ondansetron, granisetron) have been shown respectively to reduce dyspeptic symptoms in controlled clinical trials and are currently used in clinical practice to reduce nausea and vomiting in patients undergoing chemotherapy for cancer [11]. The effect on symptoms, however, has not been directly linked to a modification of gastric accommodation, emptying or a reduced visceral sensitivity. The lack of evidence of a link between the improvement of symptoms and the modification of gastric receptive relaxation may be due, among the various hypotheses, to the accuracy of the methods used to study this phenomenon. Gastric accommodation has mainly been studied using a barostat [12]; other techniques involve real-time ultrasonography (RUS) [13], magnetic resonance [14] and SPECT [15]. Furthermore, most studies have been performed on normal subjects and there are few data on dyspeptic patients where gastric accommodation to a meal may be disturbed [16].

In a previous study, we analysed gastric accommodation by means of RUS after distension with increasing amounts of water. A linear direct correlation was found between the size of the proximal stomach and the amount of water up to 500 ml, where a plateau was reached [17].

The aim of the study is therefore two-fold: first, to study gastric accommodation and symptoms before and after a water load of 500 ml in dyspeptic patients and normal controls measured by RUS; second, to test whether in dyspeptic patients ondansetron modifies gastric accommodation and symptoms after maximal gastric distension.

2. Patients and methods

Patients referred to our gastrointestinal division for abdominal complaints were studied. Each patient was referred because of symptoms characterized by pain or discomfort centred in the upper abdomen, early satiety, fullness, bloating and nausea. These subjects were defined as dyspeptic patients according to the Rome II Committee on functional gastrointestinal disorders [18]. Exclusion criteria included the presence of *Helicobacter pylori*, as diagnosed with the C13 urea breath test, symptoms suggestive of gastro-oesophageal reflux disease or irritable bowel disease, previous abdominal surgical interventions, positive upper gastrointestinal (GI) endoscopy and abdominal ultrasound for organic pathologies performed within one month from the study, age older than 80 and younger than 18, antibiotic, PPI or prokinetics therapy within the month preceding the study. Gastric accommodation was studied at fasting and after drinking 500 ml of water. A previous study has shown that gastric distension after drinking 500 ml of water produces appreciable differences in gastric size between dyspeptic patients in comparison with controls [17].

2.1. Determination of gastric size by RUS and symptoms evaluated

Proximal and distal stomach was evaluated by means of RUS using a real-time scanner (Aloka, Milan, Italy) with

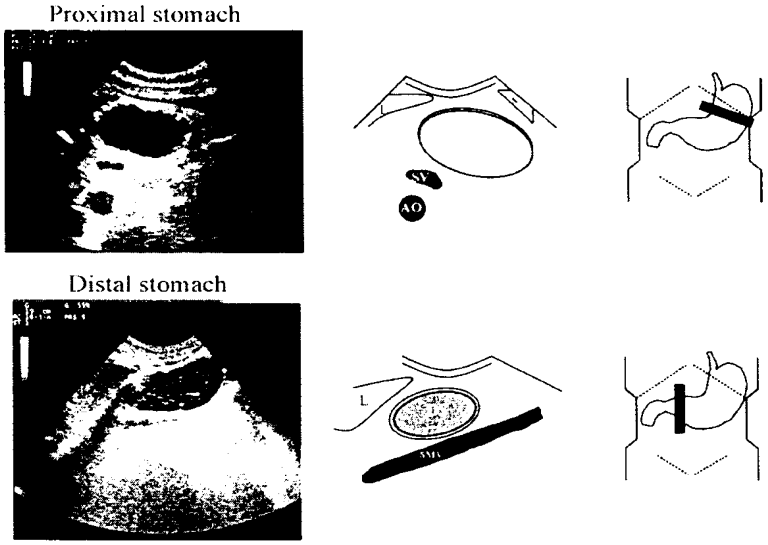

Fig. 1. Gastric proximal and distal area measured by means of real-time ultrasound after gastric distension with 500 ml of tap water in a normal human subject. AO = aorta, DS = distal stomach, PS = proximal stomach, SMV = superior mesenteric vein, SV = splenic vein.

Table 1
Symptoms score (VAS; mm) in 21 dyspeptic patients with placebo and ondansetron after 500 ml of water (mean ± S.E.M.)

Symptom	Placebo	Ondansetron	t	p
Fullness	58 ± 3.9	56 ± 2.8	0.98	ns
Epigastric pain	36 ± 2.3	34 ± 2.4	0.12	ns
Nausea	61 ± 3.6	30 ± 2.4	3.5	<0.01

a 3.5 MHz curved array transducer. All patients were studied after an overnight fast. The image of the distal stomach was taken at the epigastrium through a longitudinal scan in which it appears as an ellipse. Scans were always taken in the same position using the aorta or the superior mesenteric vein as a reference point. The proximal stomach image was taken using a transverse oblique scan at the left hypocondrium using the splenic vein as a reference point (Fig. 1). The maximum antero-posterior (AP) and transverse (LL) diameters of the proximal and distal stomach were determined before and immediately after the ingestion of 500 ml of water that was drunk in a 2-min period. The area was computed using the formula AP × LL/2. The measurements of the distal stomach were performed between contractions, when present, while the subject or patient suspended their breathing in expiration.

In two subsequent sessions in the same dyspeptic patients gastric size was measured after drinking 500 ml of water preceded by a single dose of ondansetron (8 mg i.v. 15 min before the water load) or placebo. Ondansetron or placebo was administered in a random manner at 48-h intervals in-between. RUS was performed by one of us (GC) who was unaware of the type of substance administered.

The symptoms evaluated were fullness, epigastric pain and nausea and they were scored on a visual analogue scale (VAS) of 100 mm (Table 1).

All patients gave their written informed consent to the study, which was approved by the Ethics Committee of G. D'Annunzio University.

2.2. Data analysis

The differences in gastric size (proximal and distal) at fasting and after the water load between controls and dyspeptics were evaluated using Kruskal–Wallis statistics. In dyspeptic patients, gastric areas and symptom intensity recorded after the first water load and after placebo or ondansetron were compared using a paired t-test, and confirmed through Wilcoxon matched-pairs signed-ranks test. Stata software, version 8.2, was used for all analyses (Stata Corporation, College Station, TX, USA; 2003). Data are presented as mean ± standard error of the mean (S.E.M.).

3. Results

Twenty-one dyspeptic patients (16 F, 6 M, mean age 32.6 ± 10.4 years, mean height 167 ± 11 cm, mean weight 68 ± 8 kg) and 26 normal controls (17 F, 9 M, mean age 33.3 ± 9.2 years, mean height 165 ± 10 cm, mean weight 66 ± 7.4 kg) were studied.

As shown in Fig. 2, fasting gastric size, either proximal or distal, was similar in controls and dyspeptics. Compared with controls, a significantly smaller area of the proximal stomach was visible in dyspeptic patients (dyspeptics: 14.7 ± 1.2 cm^2, controls: 18.6 ± 1.4 cm^2; $p = 0.0247$), whereas the areas of the distal stomach were similar (dyspeptics: 9.7 ± 0.8 cm^2, controls: 11.09 ± 0.6 cm^2; $p = 0.216$, Fig. 2).

In dyspeptics, gastric size (proximal and distal area) did not change following placebo (Fig. 3), whereas after the administration of ondansetron the area of the proximal and distal stomach significantly increased (proximal stomach: 14.6 ± 1.6 cm^2 placebo, 20.4 ± 1.9 cm^2 ondansetron, $p = 0.0095$; distal stomach: 8.9 ± 0.9 placebo, 11.4 ± 1.2 cm^2 ondansetron, $p = 0.0409$; Fig. 3).

In 13 dyspeptic patients (61.9%) the area of the proximal stomach was below the lower limit of the controls (15.8 cm^2, lower 95% CI), suggesting an impaired proximal gastric accommodation. When the effect of ondansetron and placebo were analysed separately (i.e. patients with reduced gastric accommodation (13 patients) and patients with gastric accommodation within the range of controls (8 patients)), gastric size increased significantly only in the group with impaired gastric accommodation ($p = 0.0071$; Fig. 4).

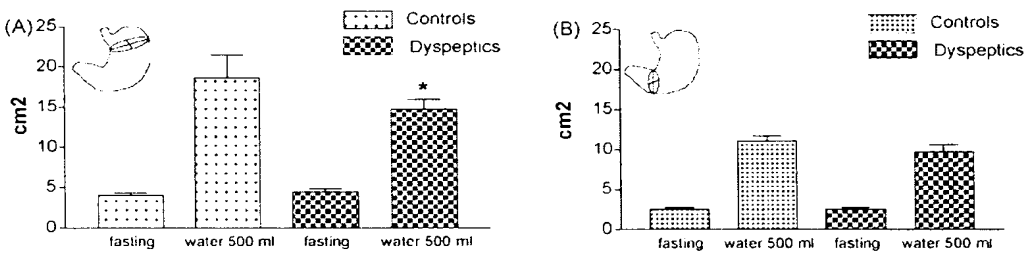

Fig. 2. Bar graph of proximal (A) and distal (B) area measured by real-time ultrasound before and after 500 ml of water in 21 dyspeptic patients and 26 normal controls (*$p < 0.05$ vs. controls).

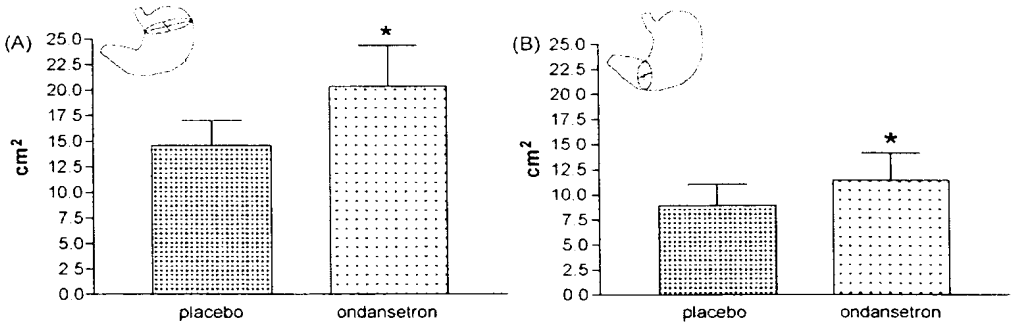

Fig. 3. Proximal (A) and distal (B) gastric area measured by means of real-time ultrasound after 500 ml of water in 21 dyspeptic patients with placebo and ondandetron 8 mg i.v. (*$p < 0.001$ vs. placebo).

4. Discussion

The main finding of this study is that ondansetron improves gastric accommodation after liquid ingestion in dyspeptic patients with reduced proximal gastric accommodation.

An impaired fundic accommodation in response to a meal has been reported in 40–60% of patients with functional dyspepsia and in several other upper gastrointestinal disorders, such as diabetic gastropathy [13], and post-fundoplication syndrome [19]. The mechanism of impaired accommodation, however, is not clearly understood and several hypotheses proposed so far involve the gastric intrinsic nitrergic neurons [20] or an abnormal vagal reflex, since post-vagotomy patients have impairment of gastric accommodation as well [2]. 5-HT3 receptors have been shown to modulate intrinsic cholinergic neurons in the gut myoenteric plexus [21] and seem to be involved in gastric (proximal and distal) motility, however, to date, contrasting results have been published on this topic. Our study is the first to show a variation of proximal gastric accommodation after a 5-HT3 receptor antagonist in association with an improvement of nausea in patients with functional dyspepsia. Previous studies on the same issue in normal subjects and in patients with dyspepsia failed to show an association between the reduced symptoms score observed after ondansetron [22], alosetron [23,24] and tropisetron [25] with no modification of gastric volumes or compliance. This leads to the hypothesis that the beneficial effects of the 5-HT3

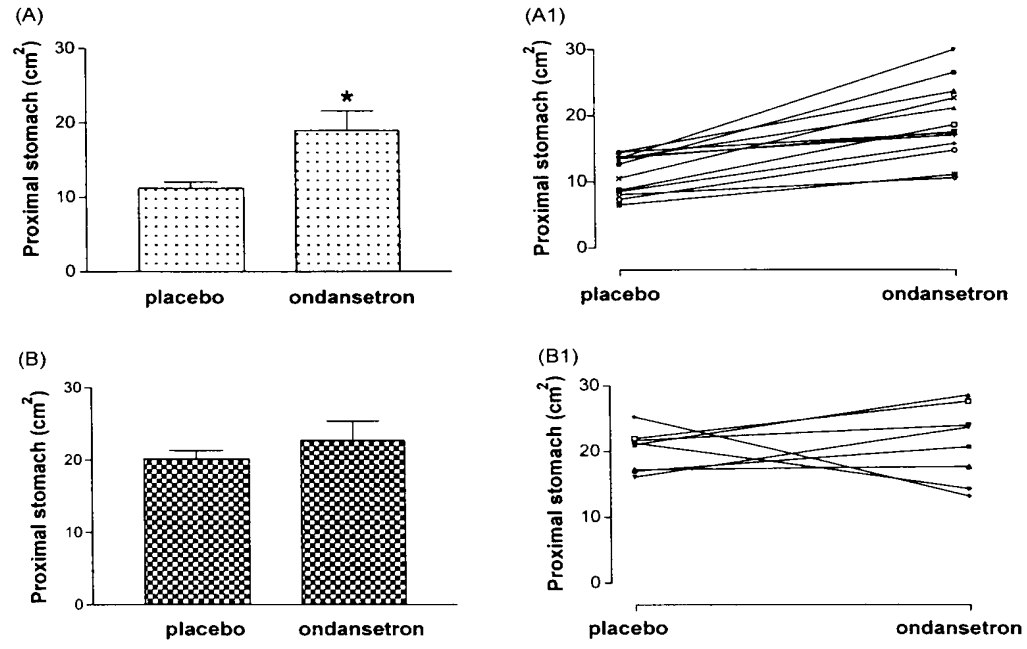

Fig. 4. Area of the proximal stomach in 13 dyspeptic patients with impaired accommodation (A: mean ± S.E.M., A1: single values) and in 8 dyspeptic patients (B: mean ± S.E.M., B1: single values) with accommodation within the range of controls, measured after the ingestion of 500 ml of water with placebo and ondansetron (8 mg i.v.).

receptor antagonist could be applied at the extrinsic afferent fibres or at central levels. The characteristics of the patients and subjects examined may partially explain the lack of efficacy of 5-HT3 antagonists found in the cited studies above. Indeed, in these studies, the 5-HT3 receptor antagonist was administered to dyspeptic patients generically considered as a whole group, without further separation into those with impaired and those with normal accommodation such as performed in our study. In patients with a correct accommodation this could not be enhanced using a 5-HT3 antagonist. In line with this hypothesis, in our study the increased gastric accommodation after ondansetron was particularly evident (and significant) in dyspeptic patients with reduced gastric accommodation, in contrast to those with the proximal area of the stomach within the normal range.

It is worth noting, however, that the method we used to evaluate gastric accommodation could also account for the differences previously cited between the present studies and other similar studies: RUS in our study, barostat and SPECT in the other studies. In a previous study using RUS, we have shown that in normal human subjects gastric size when distended with increasing amounts of liquids increases progressively up to 500 ml. If greater volumes of liquids are ingested the size does not alter [17]. The barostat is more reliable in investigating the tone of the gastric fundus rather than volume [12]. However, it is an invasive technique since it necessitates the placement of a flaccid balloon in the proximal stomach, a condition that is certainly unphysiological and is impractical when the same patient or subject is studied in multiple sessions. SPECT is a scintigraphic technique that seems well suited to measure gastric accommodation and tone [26]. However, SPECT determines a single volume value extrapolated from data collected during a 10-min period, a condition that implies that changes in volume within this period cannot be appropriately recorded. RUS is a non-invasive technique that, although it is operator dependent, may be applied with validity for the study of gastric accommodation in normal controls and in the disease state [27] and also in the evaluation of pharmacological intervention [28]. In addition, RUS is safe, non-toxic, does not necessitate chemical or radioactive contrast media, and may be repeated several times in the same subject or patient. In the authors' opinion RUS is therefore more reliable than the other techniques when gastric size is to be measured after a liquid ingestion.

Among the symptoms evaluated, only nausea improved significantly in all dyspeptic patients after ondansetron independent of the effect on gastric accommodation. This was an expected effect due to the well-known location of 5-HT3 receptors at the vomiting centres and at peripheral enteric sites [29]. This result, therefore, does not definitely rule out whether gastric fundic disaccommodation, found in our patients, is linked to the generation of symptoms. Further studies using more selective peripheral 5-HT3 receptor antagonists are necessary to clarify this issue.

From a clinical point of view our findings, in addition to previous data that have shown a beneficial effect of ondansetron 4 mg three times daily for four weeks on dyspeptic symptoms [30], warrant more placebo-controlled studies using ondansetron orally before a caloric meal in patients affected by functional dyspepsia and with reduced gastric accommodation.

In conclusion, this study shows that the 5-HT3 receptor antagonist ondansetron influences gastric accommodation in dyspeptic patients with reduced accommodation after distension, and suggests a role for 5-HT3 receptors in the accommodation process of the gastric fundus in humans.

Practice points

- The disaccommodation of the gastric fundus after food ingestion may be considered of primary importance in functional dyspepsia. The diagnosis of this abnormality may be performed by means of real-time ultrasonography, since it gives results similar to the ones obtained with a barostat.
- Among the various drugs used to treat functional dyspepsia, 5-HT3 receptor antagonists have been proposed as potentially useful by several authors. Indeed, some of these drugs are already used to treat nausea and vomiting in patients with cancer undergoing chemotherapy, while their routine use in functional dyspepsia has not been recommended yet.

Research agenda

- Gastric accommodation may be deranged in dyspeptic patients with symptoms such as early satiety, nausea and vomiting. It is not known however, whether the altered gastric function is in someway linked to the generation of the above cited symptoms.
- Although some substances that influence the activity of the 5-HT3 receptors are employed to treat nausea and vomiting, it is not known whether the 5-HT3 receptors present in the gastric wall may be involved in the gastric disaccommodation process.

Conflict of interest statement
None declared.

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Influence of sildenafil on gastric sensorimotor function in humans

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Sarnelli, Giovanni, Daniel Sifrim, Jozef Janssens, and Jan Tack. Influence of sildenafil on gastric sensorimotor function in humans. *Am J Physiol Gastrointest Liver Physiol* 287: G988–G992, 2004; doi:10.1152/ajpgi.00419.2003.—After a meal, the proximal stomach relaxes probably through the activation of nitrergic neurons in the gastric wall. Nitric oxide-induced smooth muscle relaxation involves activation of soluble guanylate cyclase, with cGMP production, which is then degradated by phosphodiesterase-5 (PDE-5). The aim of this study was to investigate the effect of sildenafil, a selective PDE-5 inhibitor, on fasting and postprandial proximal gastric volume and on gastric emptying rates in humans. A gastric barostat was used to study gastric compliance and perception to isobaric distension in healthy subjects before and after placebo (n = 13) or sildenafil, 50 mg (n = 15). In 10 healthy subjects, two gastric barostat studies were performed in randomized order to study the effect of placebo or sildenafil on postprandial gastric relaxation. Similarly, solid and liquid gastric emptying rates were studied in 12 healthy subjects. Sildenafil significantly increased fasting intragastric volume (141 ± 15 vs. 163 ± 15 ml, $P < 0.05$) and volumes of first perception. Sildenafil induced a higher and prolonged gastric relaxation either at 30 min (357 ± 38 vs. 253 ± 42 ml, $P < 0.05$) or 60 min (348 ± 49 vs. 247 ± 38 ml, $P < 0.05$) after the meal. Sildenafil did not alter solid half-emptying time but significantly delayed liquid emptying (43 ± 4 vs. 56 ± 4 min, $P < 0.01$). In conclusion, sildenafil significantly increases postprandial gastric volume and slows liquid emptying rate, confirming that meal-induced accommodation in humans involves the activation of a nitrergic pathway. The effect of sildenafil on gastric fundus suggests a therapeutic potential for phosphodiesterase inhibitors in patients with impaired gastric accommodation.

nitric oxide; gastric accommodation; gastric sensitivity; gastric emptying

DURING FASTING, muscle fibers of the proximal stomach maintain a tonic contractile activity, which is dependent on vagally mediated cholinergic input (1, 2). During and after ingestion of a meal, a relaxation of the proximal stomach occurs, which provides the food and liquids with a reservoir and enables a volume increase without a rise in pressure.

Previous studies, both in animals and in humans, have established that this accommodation reflex involves the activation of inhibitory nitrergic neurons in the gastric wall (3, 4, 13, 16, 21, 26, 37). Recent studies have established that impaired accommodation to a meal is a major pathophysiological mechanism in functional dyspepsia (14, 31, 42), and restoration of accommodation is considered a valid therapeutic target (12, 38). One way to achieve this goal would be to enhance the effect of activation of gastric nitrergic neurons.

Nitric oxide-induced smooth muscle relaxation involves the activation of soluble guanylate cyclase, leading to cGMP production (9). Sildenafil is an inhibitor of the cGMP-specific phosphodiesterase-5 (PDE-5), which breaks down cGMP. In the presence of sildenafil, nitric oxide-induced cGMP accumulates, without a concomitant increase in the concentration of nitric oxide (10, 28). Originally used in the treatment of male erectile dysfunction, recent observations demonstrate that this drug is also able to affect nitrergic control of esophageal and gastroduodenal motility in humans (5, 7, 15).

Hypersensitivity to gastric distension and delayed gastric emptying are two other pathophysiological mechanisms in functional dyspepsia (32, 33, 36). Studies using a nitric oxide synthase (NOS) inhibitor in humans did not reveal a major role of nitric oxide in the control of sensitivity to gastric distension (21, 37). In neuronal NOS-deficient mice, gastric emptying is strongly delayed, but the role of nitric oxide in the control of gastric emptying in humans has largely remained unexplored (18, 20, 34, 43).

The aim of the present study was to investigate the effect of sildenafil on proximal gastric sensory and motor function, using an electronic barostat in healthy subjects. In addition, to gain further insight into the involvement of nitric oxide in the control of gastric emptying, we also studied the effect on solid and liquid gastric emptying rate.

MATERIALS AND METHODS

Subjects

Forty-two healthy volunteers (27 men and 17 women, aged 19–29 yr, body mass index 19.7 ± 0.7) participated in the study. None of the subjects had symptoms or a history of gastrointestinal disease or drug allergies, nor were they taking any medication. Written informed consent was obtained from each participant. The protocol was approved by the Ethics Committee of the University Hospital.

Barostat Recording Technique

After an overnight fast of at least 12 h, a double-lumen polyvinyl tube (Salem sump tube 14 Charriere Sherwood Medical, Petit Rechain, Belgium) with an adherent plastic bag (1,200 ml capacity; 17-cm maximal diameter) finely folded was introduced through the mouth and secured to the subject's chin with adhesive tape. The position of the bag in the gastric fundus was checked fluoroscopically.

The polyvinyl tube was then connected to a computer-driven programmable volume-displacement barostat device (Synectics Visceral Stimulator, Stockholm, Sweden). The barostat device can deliver volume ramps or pressure steps at different rates, while simultaneously monitoring pressure and volume at a sampling rate of 8 s^{-1}. Pressure is monitored within the inflation device. To unfold the intragastric bag, it was inflated with a fixed volume of 500 ml of air for 2 min with the study subject in a recumbent position and again deflated completely. After a 10-min equilibration period, the subjects

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were positioned in a comfortable sitting position, with the knees slightly bent (80°), in a bed specifically designed for that purpose.

Specific Procedure and Design

Measurement of compliance and sensitivity to gastric distension. Twenty-eight healthy subjects (15 men, age 19–29 yr) underwent a gastric barostat study to evaluate the influence on gastric compliance and on sensitivity to gastric distension of placebo or sildenafil. Sildenafil was administered in a single-blind fashion by a nurse who was otherwise not involved in the protocol. Data analysis was done in a blinded fashion.

After a 30-min adaptation period, minimal distending pressure (MDP) was determined by increasing intrabag pressure by 1 mmHg every 3 min until a volume of ≥30 ml was reached (29). This pressure level equilibrates the intra-abdominal pressure. Subsequently, a first series of isobaric distensions was performed in stepwise increments of 2 mmHg starting from MDP, each lasting for 2 min, while the corresponding intragastric volume was recorded. Subjects were instructed to score their perception of upper abdominal sensations induced by each distending stimulus at the end of every distending step, using a graphic rating scale that combined verbal descriptors on a scale graded from 0 to 6 (29). The type of sensation was not evaluated. The end point of each sequence of distensions was established at an intrabag volume of 1,000 ml or when the subjects reported discomfort or pain (score 5 or 6).

After another 30-min adaptation period, the pressure level was set at MDP + 2 mmHg. We recorded intrabag volume 30 min before and 45 min after the oral administration of placebo or sildenafil (50 mg). Afterward, intrabag pressure was set again at MDP and a second series of stepwise isobaric distensions was performed to score perception again.

Measurement of postprandial gastric volume. Ten healthy subjects (5 men, aged 21–29 yr) underwent two gastric barostat studies, 7–20 days apart. After introduction of the bag and an adaptation period, MDP was determined as described above. Isobaric tone measurements at MDP + 2 mmHg were performed 45 min before and 60 min after a liquid meal (200 ml, 300 kcal, 13% proteins, 48% carbohydrates, 39% lipids, Nutridrink, Nutricia, Bornem, Belgium). Twenty minutes before the meal, placebo or sildenafil (50 mg) was administered in a randomized double-blind fashion.

Gastric emptying studies. In 12 healthy subjects (7 men, aged 19–29 yr), gastric emptying rate for solids and liquids was assessed twice using the previously validated [^{14}C]octanoic acid /[^{13}C]glycin breath tests (25, 32). The test meal consisted of 60 g of white bread and one egg, the yolk of which was dosed with 74 kBq of [^{14}C]octanoic acid sodium salt. The meal was ingested within 10 min, immediately followed by 150 ml of water dosed with 100 mg of [^{13}C]glycin. The total caloric value of the test meal was 250 kcal. Breath samples were taken before the meal and at 15-min intervals for 240 min postprandially. Twenty minutes before the meal, placebo or sildenafil (50 mg) was administered in a randomized double-blind fashion.

Data Analysis

For each 2-min distending period, the intragastric volume was calculated by averaging the recording. Perception threshold was defined as the first level of pressure and the corresponding volume that evoked a perception score of 1 or more. Discomfort threshold was defined as the first level of pressure and the corresponding volume that provoked a score of 5 or more. Pressure thresholds were expressed as pressures relative to MDP.

Pressure-volume and pressure-perception curves were obtained from the stepwise distensions and fitted with a linear regression model as previously described (35, 36, 38). Gastric compliance was calculated as the slope and the intercept of the pressure-volume curve obtained during at least the first three steps of isobaric distensions.

The mean intragastric volume was measured at 5-min intervals. The effect of sildenafil or placebo was quantified as the difference between the average volumes 30 min before and 45 min after administration of the drug.

Changes in intraballoon volume before and after administration of the meal were measured by calculation of the mean balloon volume for consecutive 5-min intervals. The meal-induced gastric relaxation was quantified as the difference between the average volumes during 30 min before and, respectively, 30 and 60 min after the administration of the meal. In addition, the maximum 5-min volume recorded after the meal was compared with the average volume before the meal.

Gastric half-emptying time ($t_{1/2}$) for liquids and solids was determined as previously described (25, 32).

Statistical Analysis

The sample size for the measurement of postprandial volume and gastric emptying (10 and 12 subjects, respectively) was based on one-sample *t*-test for a two-sided $\alpha = 0.05$ and $\beta = 0.20$ (80% power). Because we aimed to assess whether sildenafil has potential clinical effects, the studies were powered to demonstrate an effect size of meal-induced relaxation of 40% and of gastric emptying rate of 30%. For the study of compliance and sensitivity to gastric distension, the sample size was calculated by a two-sample *t*-test ($\alpha = 0.05$, $\beta = 0.20$, 80% power) to have clinically meaningful effects of 45% for sensitivity thresholds and gastric compliance, respectively, and of 55% for gastric volume.

The meal-induced accommodation and the gastric half-emptying times after sildenafil or placebo were compared by Student's *t*-test.

Gastric compliance, sensitivity to distension, and fasting intragastric volume, before and after administration of placebo or sildenafil, were analyzed by ANOVA for repeated measures. The Student's *t*-test was used to compare the effect of placebo and sildenafil. All statistical analysis was performed with SPSS 10.0 for Microsoft Windows. Differences were considered to be significant at the 5% level. All data are given as means ± SE.

RESULTS

Fasting Intragastric Volume and Perception of Gastric Distension

Twenty-eight volunteers were administered sildenafil (n = 15, MDP = 7.9 ± 0.4 mmHg) or placebo (n = 13, MDP = 7.8 ± 0.2 mmHg) to evaluate the effect on fasting fundic tone in a single-blind manner. The average intragastric volume at MDP + 2 mmHg, as measured by the barostat, remained unchanged before and after administration of placebo [206 ± 18 vs. 182 ± 22 ml, not significant (NS)]. In the subjects receiving sildenafil, the average intragastric volume at MDP + 2 mmHg significantly increased from 140.7 ± 15 to 162.6 ± 15 ml after the drug ($P = 0.03$).

Both before and after the administration of placebo or sildenafil, distensions of the stomach with progressively higher set pressures produced progressively larger intragastric volumes. Placebo did not alter the intragastric volumes for the same distending pressure. Administration of placebo did not alter the slope (54 ± 7 vs. 57 ± 12 ml/mmHg, NS) and the y-intercept (128.6 ± 23 vs. 85 ± 49 ml, NS) of the pressure-volume curve obtained after linear model fitting. At the same distending pressures, intragastric volumes after sildenafil were significantly larger than the corresponding volumes before

drug administration (Fig. 1). The slope of the pressure-volume curves, obtained after linear model fitting, was not altered by sildenafil (61.6 ± 8.4 vs. 61.5 ± 6 ml/mmHg, NS), whereas the *y*-intercept of the pressure-volume curves was significantly increased after sildenafil (17 ± 22 vs. 122 ± 42 ml, $P = 0.01$). This shift of the pressure-volume curve toward higher volumes probably reflects a sildenafil-induced relaxation of the gastric fundus.

Placebo did not affect the pressure inducing first perception (2.9 ± 0.4 vs. 3.3 ± 0.3 mmHg above MDP, NS) or discomfort pressure (10.7 ± 0.8 vs. 10 ± 0.6 mmHg above MDP, NS), and the corresponding intra-balloon volumes were not altered (first perception: 275 ± 29 vs. 287 ± 29 ml; discomfort: 652 ± 47 vs. 618 ± 50 ml) (all NS).

Sildenafil also had no significant influence on the pressure levels inducing first perception (3.3 ± 0.3 vs. 3.1 ± 0.3 mmHg above MDP, NS) or discomfort (10 ± 0.6 vs. 8.4 ± 0.6 mmHg above MDP, NS). However, the corresponding volume at the thresholds for first perception (234 ± 39 vs. 336 ± 41 ml, $P = 0.02$) and at the thresholds for discomfort (561 ± 39 vs. 633 ± 38 ml, $P = 0.05$) was significantly increased by sildenafil.

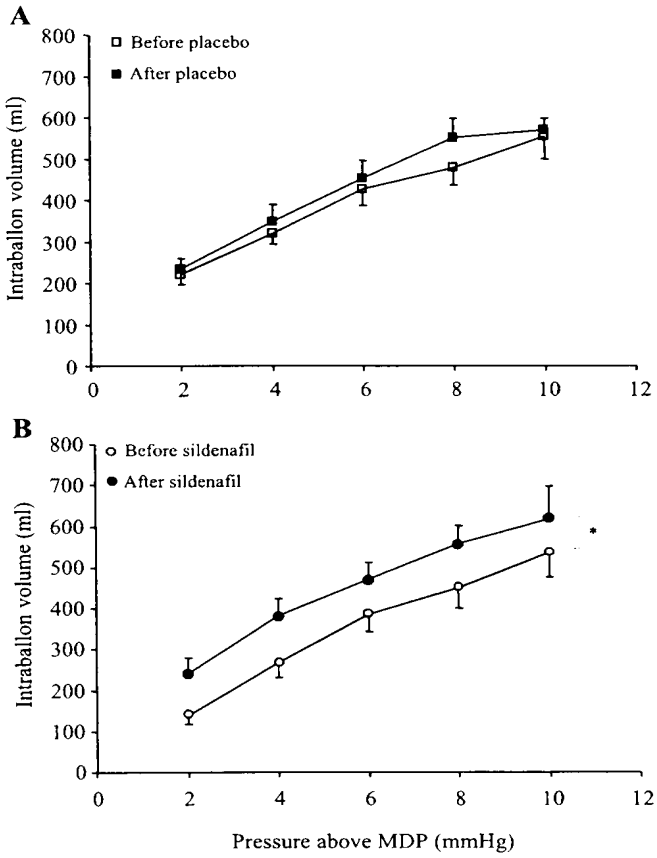

Fig. 1. Pressure-volume relation obtained by gradually increasing isobaric gastric distensions before and after placebo (*A*) and sildenafil (50 mg) (*B*). Linear model fitting revealed that placebo does not significantly affect the curve, whereas the sildenafil causes a shift of the pressure-volume curve to significantly higher volumes (*$P < 0.05$). MDP, minimal distending pressure.

Postprandial Intragastric Volume

The effect of placebo or sildenafil on postprandial intraballoon volume was assessed in 10 volunteers. MDPs (7.5 ± 0.3 vs. 7.8 ± 0.2 mmHg, NS) and preprandial intragastric volumes (176 ± 20 vs. 154 ± 22 ml, NS) were similar in both groups.

Ingestion of the meal caused an immediate relaxation of the proximal stomach in all subjects, reflected by an increase in the balloon volume (Fig. 2). However, after administration of sildenafil, a higher gastric relaxation was observed during the first 30 min (357 ± 38 vs. 253 ± 42 ml, $P < 0.05$) and 60 min after the meal (348 ± 49 vs. 247 ± 38 ml, $P < 0.05$). In addition, sildenafil significantly increased the maximum postprandial volume (444 ± 51 vs. 338 ± 48 ml, $P < 0.05$), whereas the time to maximum postprandial volume was not significantly different (43.5 ± 3.0 vs. 52 ± 5.4 min, NS).

Gastric Emptying

Sildenafil induced a significant delay of liquid gastric emptying ($t_{1/2}$ 43 ± 4 vs. 56 ± 4 min, $P < 0.01$, Fig. 3), whereas solid emptying was not significantly affected ($t_{1/2}$ 65 ± 6 vs. 66 ± 4 min, NS).

DISCUSSION

We used sildenafil, a selective PDE-5 inhibitor, to study the involvement of nitrergic neurons in the control of fasting and postprandial gastric tone, of gastric sensitivity to distension, and of gastric emptying in humans.

In the interdigestive state, administration of sildenafil causes a significant relaxation of the gastric fundus: at the same intragastric pressure, larger intragastric volumes are present and consequently larger volumes are needed before thresholds for perception or discomfort are reached. In the postprandial state, pretreatment with sildenafil significantly enhanced gastric accommodation to a meal and delayed liquid gastric emptying.

Nitric oxide is the principal inhibitory transmitter at the neuromuscular junction in the gastrointestinal tract, and its mechanism of action involves cGMP production by soluble guanylate cyclase in smooth muscle cells. Sildenafil inhibits the PDE-5, thereby allowing the accumulation of the nitric oxide-induced cGMP and enhancing the physiological effects of nitric oxide (10). During fasting, the proximal stomach is in a continuous state of tonic contraction that is maintained by a vagally mediated cholinergic input (3, 23). In the cat, administration of the nitric oxide synthase inhibitor N^G-nitro-L-arginine methyl ester results in an increase of the resting fundus tone, an effect that is reversed by L-arginine, suggesting that resting fundus tone in this species is maintained by the balance of a cholinergic and a nitrergic drive (11). Fasting gastric tone in humans is susceptible to nitric oxide, because the administration of a nitric oxide donor induces a proximal gastric relaxation (40). Here we provide further evidence of the contribution of a nitrergic drive to resting fundus tone in humans. Sildenafil significantly increased interdigestive intragastric volumes and shifted the pressure-volume curve toward higher volumes. In keeping with this observation, it can be hypothesized that the inhibition of cGMP degradation enhances the effects of the nitric oxide physiologically released at

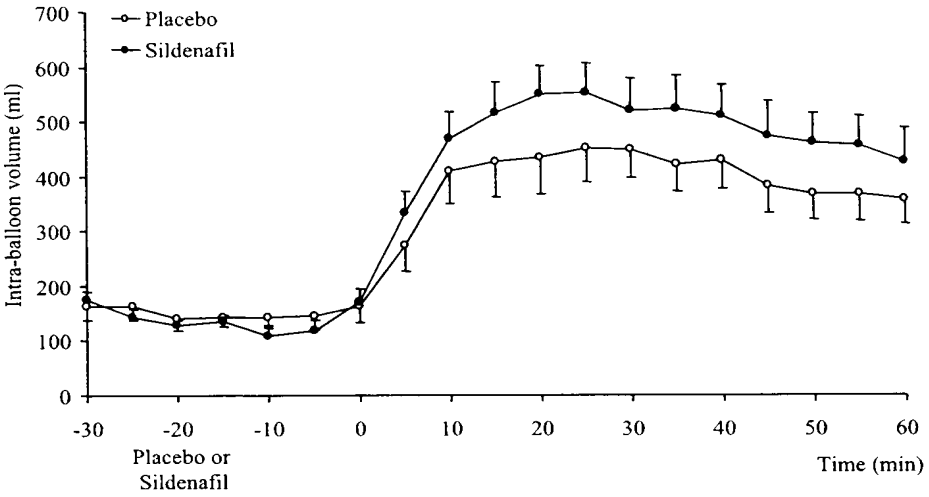

Fig. 2. Mean intragastric volume at 5-min intervals as measured by gastric barostat in 10 healthy volunteers before and after administration of a liquid meal (time = 0). Twenty minutes before the meal, placebo or sildenafil (50 mg) was administered in a randomized double-blind fashion (time = −20). Ingestion of the meal induces a rapid and marked fundus relaxation that is significantly larger after sildenafil than placebo.

the level of nitrergic neurons of the gastric wall, which would in turn result in the sildenafil-induced gastric relaxation.

Sildenafil significantly affected the gastric sensitivity to isobaric distensions and caused a significant increase in the volumes needed to reach the thresholds for discomfort. Because the drug did not alter the pressure-expressed sensory thresholds, it seems likely that the decrease in tone is the principal effect of sildenafil and that the higher volume thresholds are most likely occurring secondary to the sildenafil-induced relaxation.

Postprandial intragastric volumes were significantly enhanced by pretreatment with sildenafil, suggesting that meal-induced accommodation in humans involves the activation of a nitrergic pathway (16, 38). Gastric relaxation is mediated through a vagovagally driven nonadrenergic noncholinergic (NANC) mechanism (2). Both in vivo and in vitro studies suggest that the principal candidate neurotransmitters released by NANC neurons during gastric accommodation are nitric oxide and vasoactive intestinal polypeptide (4, 6, 7, 13, 22, 26, 41). Depending on the species studied, both inhibitory neurotransmitters can act concurrently in mediating NANC relaxations of the fundus (6, 22, 39, 41), or nitric oxide can be the only mediator of the NANC relaxation (13, 26, 27). Enhancement of meal-induced gastric relaxation by sildenafil suggests involvement of nitric oxide in the gastric accommodation reflex in humans, and this observation is in agreement with our previous observation that nitric oxide synthase inhibition significantly inhibits gastric accommodation in humans (37).

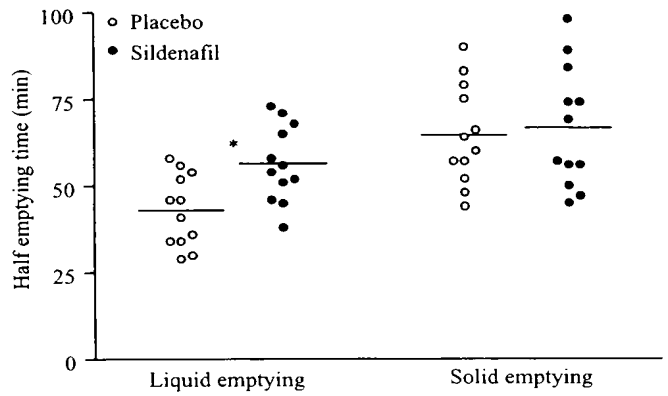

Fig. 3. Effect of sildenafil or placebo on the half-emptying time ($t_{1/2}$) of the solid and liquid phases of the meal (n = 12 subjects): $t_{1/2}$ for liquid emptying was significantly delayed after sildenafil compared with placebo (*$P < 0.01$).

After sildenafil, higher intragastric volumes were recorded up to 60 min after the meal, suggesting that sildenafil also prolongs meal-induced fundus relaxation. Several studies have shown involvement of recovery in proximal gastric tone as a drive for gastric emptying, especially of liquids (8, 17, 30). The delay in liquid emptying observed after pretreatment with sildenafil probably reflects this postponed recovery of postprandial proximal gastric driving force. Sildenafil did not seem to affect solid gastric emptying. Although a limiting factor for solid emptying may be solid grinding, which may not have been affected by nitrergic modulation, enhanced pyloric sphincter relaxation with a diminished outflow resistance, compensating for the decreased driving force of the proximal or distal stomach, is an alternative explanation (19, 24). Using the dual-emptying breath test, emptying rates for liquids are relatively slow. This may be attributed both to the glycin content of the liquid meal and to the simultaneous administration with a solid meal (25, 32).

Previous studies have suggested a therapeutic potential for phosphodiesterase inhibitors in gastrointestinal disorders such as achalasia or diabetic gastroparesis (5, 43). The current study also indicates a therapeutic potential of phosphodiesterase inhibitors in patients with impaired accommodation of the proximal stomach to a meal (14, 38). Studies investigating its potential in these patients seem warranted.

In conclusion, we showed that sildenafil affects proximal stomach motility in normal subjects. The drug increases proximal gastric compliance during the fasting state and enhances gastric accommodation to a meal. Furthermore, administration of sildenafil causes a delay in the emptying of liquids. Our results suggest the presence of a nitrergic tonic inhibitory influence on proximal gastric tone during fasting. They also confirm that meal-induced accommodation in humans involves

the activation of a nitrergic pathway and suggest a therapeutic potential for phosphodiesterase inhibitors in patients with impaired gastric accommodation.

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Role of Impaired Gastric Accommodation to a Meal in Functional Dyspepsia

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See editorial on page 1586.

Background & Aims: Impaired accommodation of the proximal stomach to a meal has been reported in functional dyspepsia, but its relevance to symptoms is unclear. The aim of this study was to test the hypothesis that impaired gastric accommodation causes early satiety. *Methods:* A gastric barostat was used to study postprandial fundus relaxation in 35 healthy subjects and 40 patients with functional dyspepsia. Gastric emptying, *Helicobacter pylori* status, sensitivity to gastric distention, and a dyspepsia symptom score were obtained from all patients. In addition, the effect of sumatriptan, a fundus-relaxing 5-hydroxytryptamine$_1$ agonist, on gastric accommodation and on early satiety in dyspeptic patients was studied. *Results:* Impaired gastric accommodation to a meal was found in 40% of the patients. In univariate analysis, this was associated with early satiety and weight loss but not with hypersensitivity to gastric distention, presence of *H. pylori*, or delayed gastric emptying. In a multivariate analysis, only early satiety was associated with impaired gastric accommodation. Sumatriptan restored gastric accommodation, thereby significantly improving meal-induced satiety. *Conclusions:* Impaired relaxation of the proximal stomach to a meal is present in a high proportion of patients with functional dyspepsia. It is associated with symptoms of early satiety. Restoring gastric accommodation with a fundus-relaxing drug improves early satiety.

Functional dyspepsia is a clinical syndrome defined by chronic or recurrent upper abdominal symptoms without identifiable cause by conventional diagnostic means.[1] The symptom complex is often related to feeding and includes epigastric pain, bloating, early satiety, fullness, anorexia, belching, nausea, and vomiting.[2] The pathophysiology of functional dyspepsia is unknown, but it has been suggested that dyspeptic symptoms could originate from delayed gastric emptying, visceral hypersensitivity to distention, abnormal duodenojejunal motility, *Helicobacter pylori* gastritis, or central nervous system dysfunction.[2-9] No consistent correlation between symptoms and impaired function has been identified.

Accommodation of the stomach to a meal consists of a relaxation of the proximal stomach, providing the meal with a reservoir and enabling a volume increase without an increase in pressure. Recent studies have shown an abnormal intragastric distribution of food in patients with functional dyspepsia, with preferential accumulation in the distal stomach, suggesting defective postprandial relaxation of the proximal stomach.[8,10-12] Barostat and ultrasonography studies of the proximal stomach confirmed impaired accommodation to a meal in patients with functional dyspepsia.[10,13] It is unclear whether impaired postprandial relaxation is causing symptoms in patients with functional dyspepsia. In view of the role of gastric accommodation in providing a reservoir during meal intake, absence of normal accommodation is likely to induce early satiety.

The aim of the present study was to show that impaired gastric accommodation to a meal is associated with symptoms of early satiety. This would imply that restoring gastric accommodation is improving symptoms of early satiety. To investigate this latter hypothesis, we developed a test to quantify meal-induced satiety, and we used the fundus-relaxing properties of the 5-hydroxytryptamine$_1$ (5-HT$_1$) receptor agonist sumatriptan to enhance gastric accommodation.[14,15]

Materials and Methods

Study Subjects

Thirty-five healthy controls (24 men and 11 women; age, 19–34 years; mean age, 24.2 ± 0.6 years) and 40 patients with functional dyspepsia (12 men and 28 women; age, 17–69 years; mean age, 38.4 ± 2.1 years) participated in the study. None of the healthy subjects had symptoms of or a history of gastrointestinal disease or drug allergies, and none of the healthy subjects were taking any medication.

The patients presented to the outpatient clinic because of meal-related epigastric symptoms, and all underwent careful

Abbreviations used in this paper: 5-HT$_1$, 5-hydroxytryptamine$_1$; MDP, minimal distending pressure; t$_{1/2}$, half-emptying time.

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history taking and clinical examination, upper gastrointestinal endoscopy, routine biochemistry, and upper abdominal ultrasonography. Inclusion criteria were the presence of dyspeptic symptoms for at least 3 months in the absence of organic, systemic, or metabolic disease. Dyspeptic symptoms had to be present at least 3 days per week, with two or more symptoms scored as relevant or severe on the symptom questionnaire (see below). Exclusion criteria were the presence of esophagitis, gastric atrophy, or erosive gastroduodenal lesions on endoscopy; heartburn as a predominant symptom; a history of peptic ulcer, major abdominal surgery, or underlying psychiatric illness; and the use of nonsteroidal anti-inflammatory drugs, steroids, or drugs affecting gastric acid secretion. During upper gastrointestinal endoscopy, biopsy specimens were taken from the antrum and the corpus to stain with cresyl violet for the presence of *H. pylori*. In patients with relevant or severe epigastric burning on the symptom questionnaire (n = 9), a 24-hour esophageal pH monitoring was performed and found to be normal (<4% of time pH of <4). Patients with a weight loss of >5% of the initial body weight were assessed by a psychiatrist to rule out anorexia nervosa. All drugs potentially affecting gastrointestinal motility were discontinued at least 1 week before the barostat and gastric emptying studies. Informed consent was obtained from each participant. The protocol had been approved previously by the Ethics Committee of the University Hospital.

Symptom Questionnaire

Before the barostat studies, each patient completed a dyspepsia questionnaire. A previously described questionnaire was used[16] with the addition of three symptoms. The patient was asked to grade the intensity (0, absent; 1, mild; 2, relevant; and 3, severe and interfering with daily activities) of eight different symptoms (epigastric pain, bloating, postprandial fullness, early satiety, nausea, vomiting, belching, and epigastric burning). Also, the amount of weight lost since the onset of the symptoms was noted.

Gastric Emptying Studies

Gastric emptying for solids was measured in all patients, using the previously validated [^{14}C]octanoic acid breath test.[17] Briefly, all studies were performed in the morning after an overnight fast. The test meal consisted of 60 g white bread, one egg, the yolk of which was doped with 74 kBq of [^{14}C]octanoic acid sodium salt, and 300 mL water. Breath samples were taken before the meal and at 15-minute intervals for a period of 240 minutes postprandially. Gastric half-emptying time ($t^1/_2$) was calculated as described previously.[15] Delayed emptying was defined as $t^1/_2$ greater than the 95% confidence interval in healthy volunteers.[18]

Barostat Studies

After an overnight fast of at least 12 hours, a double-lumen polyvinyl tube (Salem sump tube 14 Ch.; Sherwood Medical, Petit Rechain, Belgium) with a finely folded adherent plastic bag (1200-mL capacity; maximal diameter, 17 cm) was introduced through the mouth and secured to the subject's chin with adhesive tape. The position of the bag in the gastric fundus was checked fluoroscopically.

The polyvinyl tube was then connected to a programmable barostat device (Synectics Visceral Stimulator, Stockholm, Sweden). To unfold the bag, it was inflated with a fixed-volume of 300 mL air for 2 minutes with the study subject in a recumbent position, and it was again deflated completely. The subjects were then positioned in a comfortable sitting position with the knees bent (80°) and the trunk upright in a specifically designed bed.

After a 30-minute adaptation period, minimal distending pressure (MDP) was first determined by increasing intrabag pressure by 1 mm Hg every 3 minutes until a volume of ≥30 mL was reached.[19] This pressure level equilibrates the intra-abdominal pressure. Subsequently, isobaric distentions were performed in stepwise increments of 2 mm Hg starting from MDP, each lasting for 2 minutes, while the corresponding intragastric volume was recorded. Subjects were instructed to score their perception of upper abdominal sensations at the end of every distending step using a graphic rating scale that combined verbal descriptors on a scale graded 0–6.[19] The end point of each sequence of distentions was established at an intrabag volume of 1000 mL or when the subjects reported discomfort or pain (score of 5 or 6).

After a 30-minute adaptation period with the bag completely deflated, the pressure level was set at MDP + 2 mm Hg for at least 90 minutes. After 30 minutes, a liquid meal (200 mL, 300 kcal, 13% proteins, 48% carbohydrates, and 39% lipids [Nutridrink; Nutricia, Bornem, Belgium]) was administered. In all patients and in 10 healthy subjects, gastric tone measurement was continued for 60 minutes after the meal. In the other 25 healthy subjects, the measurement continued until 120 minutes after the meal.

In 6 patients with impaired gastric accommodation to the meal, the barostat study was repeated after 3–7 days with administration of 6 mg sumatriptan (Imitrex; Glaxo-Wellcome, Brussels, Belgium) subcutaneously immediately before the meal.

Satiety Testing

Ten healthy subjects and 10 patients with early satiety also underwent a test to quantify the occurrence of meal-induced satiety. A peristaltic pump (Minipuls 2; Gilson, Villiers-Le-Bel, France) filled one of two beakers at a fixed rate of 15 mL/min with a liquid meal (Nutridrink; Nutricia). The subjects were requested to maintain intake at the filling rate, thereby alternating the beakers as they were filled and emptied. At 5-minute intervals, they were asked to score their satiety using a graphic rating scale that combined verbal descriptors on a scale graded of 0–5 (1, threshold; 5, maximum satiety). Participants were instructed to stop meal intake when a score of 5 was reached. All patients underwent the satiety test twice with an interval of 3–7 days. Immediately before the test, placebo or sumatriptan 6 mg was administered subcutaneously in a randomized, double-blind way.

Data Analysis

Primary end points were the size of the meal-induced fundus relaxation, and the total calorie intake at satiety score equal to 5. Secondary end points were the thresholds for perception and discomfort during gastric distention, the rate of gastric emptying, and the *H. pylori* status.

For each 2-minute distending period, the intragastric volume was calculated by averaging the recording. Perception threshold was defined as the first level of pressure and the corresponding volume that evoked a perception score of ≥ 1. Discomfort threshold was defined as the first level of pressure and the corresponding volume that provoked a score of ≥ 5. Gastric compliance was calculated as the slope of the pressure-volume curve obtained during the stepwise isobaric distentions. Hypersensitivity to gastric distention was defined as a discomfort threshold less than the mean -2SD in healthy volunteers.

Gastric tone before and after administration of the meal was measured by calculation of the mean balloon volume for consecutive 5-minute intervals. The meal-induced gastric relaxation was quantified as the difference between the average volumes during 30 minutes before and 60 minutes after the administration of the meal. Also, the amplitude of the maximal relaxation was calculated as the difference between the average preprandial volume and the highest postprandial 5-minute interval mean volume. For the meal-induced satiety testing, the amount of calories ingested until the occurrence of maximum satiety (score of 5) was calculated.

Statistical Analysis

Barostat results in healthy subjects and patients were compared by the Student *t* test or by the Kolmogorov–Smirnov test for non-normally distributed data. The normal range (mean $\pm$ 2SD) for the meal-induced gastric relaxation was calculated from the data for healthy volunteers. Subsequently, patients were divided into those with normal and those with insufficient meal-induced relaxation. Age, body weight, gastric compliance, thresholds to gastric distention, and $t^1/_2$ for solid gastric emptying in both patient groups were compared using the Student *t* test. The relationship between meal-induced relaxation and the amount of calories at maximum satiety was evaluated by linear regression analysis. Both meal-induced relaxation and the amount of calories at maximum satiety with or without administration of sumatriptan were compared by the Student *t* test. Furthermore, individual dyspeptic symptoms were analyzed using three possible cutoffs (≥ 1 vs. 0, ≥ 2 vs. ≤ 1, and 3 vs. ≤ 2). The prevalence of dyspeptic symptoms, sex distribution, and presence of *H. pylori* infection in both patient groups were compared by χ^2 testing.

Stepwise multiple logistic regression analysis was used to identify the association between the risk of impaired postprandial gastric relaxation, presence of dyspeptic symptoms, and patient variables. *P* values of 0.05 and 0.1 were chosen as cutoff points to enter and exit the stepwise procedure. Odds ratios (ORs) with 95% confidence interval (CI) were computed. Similar statistics were performed for the relation between symptoms, patient variables, *H. pylori* status, delayed gastric emptying, and hypersensitivity to gastric distention.

Differences were considered to be significant at the 5% level. All data are given as means $\pm$ SEM. Statistical evaluations were performed using specialized software (SAS; SAS Institute, Cary, NC).

Results

Characteristics of Patients With Functional Dyspepsia

Patients with functional dyspepsia were significantly older than healthy subjects, and a higher proportion of the patients were women ($P < 0.01$). Table 1 summarizes the grading of dyspeptic symptoms in the patient group. Postprandial fullness and bloating were the most prevalent symptoms, both present in 82.5% of the patients. Epigastric pain (67.5%), early satiety (67.5%), nausea (65%), and belching (55%) were also reported frequently. Vomiting and burning sensation were present in 40% and 37.5%, respectively, of the patients. Weight loss of >5% was present in 22 patients (55%). In 11 patients (27.5%), *H. pylori* was shown on gastric biopsy specimens. Fourteen patients (35%) had delayed gastric emptying of solids ($t^1/_2$ of longer than 119 minutes).

Gastric Accommodation in Healthy Subjects and Patients

In healthy subjects, MDP was 7.4 $\pm$ 0.4 mm Hg. The preprandial intragastric balloon volume at MDP + 2 mm Hg was 178 $\pm$ 14 mL. In all volunteers, ingestion of the meal caused an immediate relaxation of the proximal stomach, reflected by an increase in the balloon volume (Figure 1). Five minutes after the meal, the intraballoon volume was significantly greater than the mean preprandial volume, and it remained significantly elevated until 115 minutes postprandially. During the first postprandial hour, the mean intraballoon volume was 401 $\pm$ 22 mL, which corresponds to an increase of 223 $\pm$ 13 mL.

Table 1. Frequency of Severity Grading for Each of Six Dyspepsia Symptoms in 40 Consecutive Patients With Functional Dyspepsia

	0 (Absent)	1 (Mild)	2 (Relevant)	3 (Severe)
Postprandial fullness	7 (17.5)	0 (0)	2 (5)	31 (77.5)
Bloating	7 (17.5)	2 (5)	4 (10)	27 (67.5)
Epigastric pain	13 (32.5)	3 (7.5)	2 (5)	22 (55)
Early satiety	13 (32.5)	3 (7.5)	5 (12.5)	19 (47.5)
Nausea	14 (35)	3 (7.5)	6 (15)	17 (42.5)
Vomiting	24 (60)	0 (0)	1 (2.5)	15 (37.5)
Belching	18 (45)	5 (12.5)	10 (25)	7 (17.5)
Epigastric burning	25 (62.5)	6 (15)	2 (5)	7 (17.5)

NOTE. Numbers in parentheses represent row percentages.

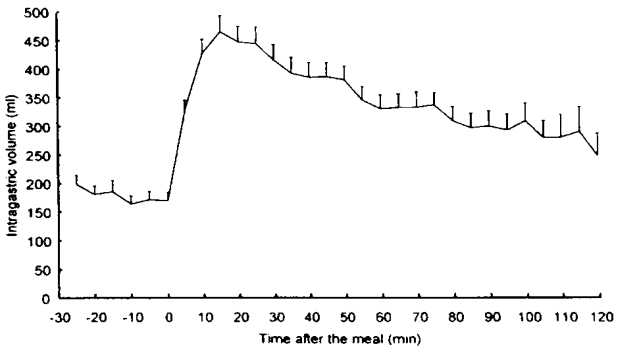

Figure 1. Mean intragastric volume at 5-minute intervals as measured by a gastric barostat in healthy volunteers before and after administration of a mixed liquid meal (time 0). Ingestion of the meal induces a rapid and sustained increase in intragastric volume, reflecting a relaxation of the gastric fundus. The number of volunteers at each data point is 35 before the meal and during the first postprandial hour and 25 for the second postprandial hour. The postprandial intragastric volume was significantly greater than the mean preprandial volume at each point from 5 to 115 minutes after the meal.

The lower range of normal (mean − 2SD) for the meal-induced increase in intraballoon volume was 64 mL (Figure 2).

In patients with functional dyspepsia, MDP was 7.0 ± 0.4 mm Hg, and the average preprandial intragastric volume at MDP + 2 mm Hg was 184 ± 15 mL (not significant compared with healthy controls). The mean balloon volume averaged during the 60 minutes after the meal was 328 ± 26 mL, reflecting an average increase in intragastric volume of 144 ± 18 mL. The mean balloon volume during the first postprandial hour, the average increase in intragastric volume, and the maximum volume increase after the meal (190 ± 24 mL vs. 337 ± 18 mL) were all significantly less than in healthy volunteers ($P < 0.01$). Using the lower range of normal in healthy volunteers (64 mL) as a cutoff, 16 patients (40%) had an impaired gastric accommodation as measured by the barostat (Figure 2).

Sensitivity to Gastric Distention in Healthy Subjects and Patients

In healthy subjects, first perception or discomfort during gastric distention was reached at distending pressures of 4.1 ± 0.5 and 12.1 ± 0.4 mm Hg above MDP, respectively. The corresponding intragastric balloon volumes were 253 ± 22 and 660 ± 34 mL, respectively. Gastric compliance was 58 ± 6 mL/mm Hg. The lower range of normal (mean − 2SD) for the distending pressure inducing discomfort was 7.1 mm Hg above MDP.

In patients with functional dyspepsia, first perception and discomfort during gastric distention were reached at pressures of 2.5 ± 0.2 and 9.1 ± 0.6 mm Hg above MDP, respectively ($P < 0.02$ compared with healthy controls). The corresponding intragastric volumes were 192 ± 19 and 496 ± 23 mL, respectively ($P < 0.05$ compared with healthy controls). Gastric compliance was 63.4 ± 7.2 mL/mm Hg (not significant compared with healthy controls). Thirteen patients (32%) had hypersensitivity to gastric distention (distending pressure inducing discomfort <7.1 mm Hg above MDP).

Univariate Analysis of Pathophysiological and Symptomatic Correlates of Impaired Postprandial Fundus Relaxation

There was no significant difference in sex distribution, body weight, height, or age between patients with impaired and with normal gastric accommodation (5 of 16 vs. 7 of 24 patients, 56 ± 3 vs. 61 ± 2 kg, 168 ± 2 vs. 168 ± 2 cm, and 34 ± 4 vs. 41 ± 2 years, respectively). The prevalence of *Helicobacter* infection also did not differ (5 of 16 vs. 6 of 24 patients). There was no difference in $t^{1}/_{2}$ for solids between both groups (116 ± 14 vs. 123 ± 17 minutes; not significant), and the prevalence of de-

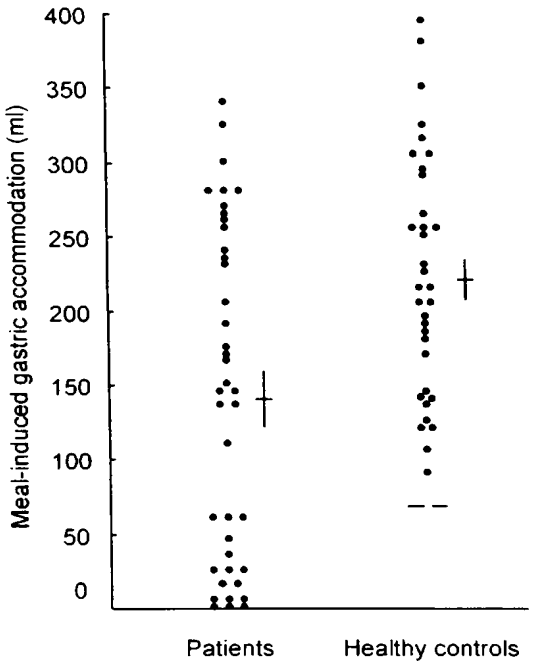

Figure 2. Gastric accommodation to a meal, quantified as the difference between the average volumes during the 30 minutes before and 60 minutes after the administration of the meal, in 40 patients with functional dyspepsia and 35 healthy controls. Individual values are shown as dots; mean and SEM for each group are shown as bars. A subset of the patients have a meal-induced gastric relaxation below the normal range, indicated by the two horizontal bars.

layed emptying for solids did not differ (4 of 16 and 9 of 24 patients; not significant). The pressure and volume thresholds inducing first perception (2.3 ± 0.2 vs. 2.6 ± 0.2 mm Hg above MDP and 233 ± 43 vs. 165 ± 13 mL; not significant) or discomfort (8.0 ± 0.7 vs. 9.8 ± 0.9 mm Hg above MDP and 537 ± 43 vs. 469 ± 25 mL; not significant) and the prevalence of hypersensitivity to gastric distention did not differ between both groups (7 of 16 and 6 of 24; not significant). Gastric compliance was similar in both patient groups (68 ± 6 vs. 57 ± 5 mL/mm Hg; not significant).

Weight loss of >5% of the initial body weight was significantly more prevalent in patients with impaired gastric accommodation (12 of 16 vs. 10 of 24 patients; $P < 0.05$). The association between individual symptom grading and impaired gastric accommodation to a meal was investigated. The presence of relevant or severe early satiety (score of ≥2) was significantly more prevalent in patients with impaired accommodation to a meal (15 of 16 vs. 9 of 24 patients; $P < 0.0005$). Figure 3 shows the percentage of patients grading individual symptoms as relevant or severe and the presence of weight loss in the subgroups with normal or impaired gastric accommodation. Similarly, the presence of early satiety (score of ≥1) and of severe early satiety (score of ≥3) was significantly more prevalent in patients with impaired accommodation (15 of 16 vs. 12 of 24 patients, $P < 0.005$; and 11 of 16 vs. 8 of 24 patients, $P < 0.05$, respectively). The prevalence of the other symptoms did not differ between both groups, regardless of the score cutoff level.

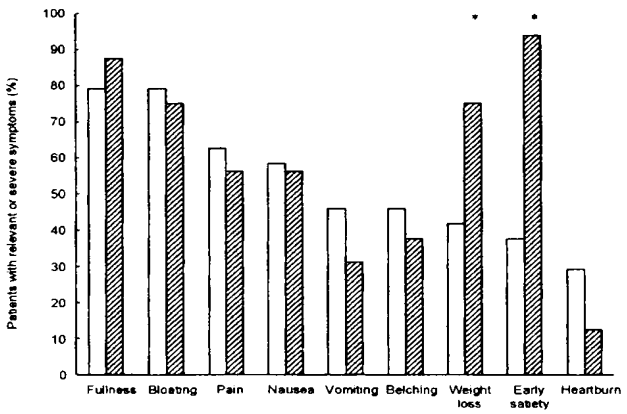

Figure 3. Dyspepsia symptoms in 40 consecutive patients with functional dyspepsia. The figure shows the number of patients grading individual symptoms as relevant or severe (score of ≥2) in the subgroups with normal (□) or impaired (▨) gastric accommodation. Early satiety and weight loss of >5% of the initial body weight were significantly more prevalent in patients with impaired accommodation to a meal.

Multivariate Analysis of Pathophysiological and Symptomatic Correlates of Impaired Postprandial Fundus Relaxation

Stepwise multiple logistic regression analysis was used to identify the association between the risk of impaired accommodation and different patient variables and symptoms. Age, sex, body weight, and height did not influence the risk of impaired postprandial gastric relaxation. When symptoms coded as relevant or severe symptoms (score of ≥2) were considered, early satiety was the only symptom that was independently associated with impaired accommodation (OR, 25; 95% CI, 4.03–491.8; $P = 0.004$). Similarly, when the presence of symptoms (score of ≥1) or the presence of severe symptoms (score of ≥3) was considered, only early satiety was significantly associated with impaired accommodation (OR, 15; 95% CI, 2.43–293.2; $P = 0.01$; and OR, 4.4; 95% CI, 1.19–18.4; $P = 0.03$, respectively). Weight loss, which was associated with impaired accommodation in the univariate analysis, and all other symptoms, were not independent factors in the multiple logistic regression.

Similar statistics were performed using *H. pylori* status, delayed gastric emptying, or hypersensitivity to gastric distention as the response variable. The only significant association obtained was between the presence of severe nausea and delayed gastric emptying (OR, 9.52; 95% CI, 2.22–52.8; $P = 0.002$). A negative association was observed between the presence of relevant or severe nausea and hypersensitivity to gastric distention (OR, 0.187; 95% CI, 0.04–0.75; $P = 0.02$).

Effect of Sumatriptan on Impaired Accommodation to a Meal

In 6 patients with impaired gastric accommodation (6 women; age, 32.7 ± 4.3 years), the gastric barostat study was repeated with administration of 6 mg sumatriptan subcutaneously before the meal. Pretreatment with sumatriptan significantly increased the meal-induced relaxation from 42 ± 22 to 116 ± 37 mL ($P = 0.005$) (Figure 4*A*).

Satiety Testing in Healthy Subjects and Patients With Functional Dyspepsia

In healthy subjects, a highly significant correlation existed between satiety scores and the amount of kilocalories ingested ($r = 0.98$; $P < 0.0001$). The amount of calories ingested until the occurrence of maximum satiety was 1028 ± 325 kcal. In healthy subjects, no correlation was found between the amount of calories ingested at maximum satiety and the amplitude

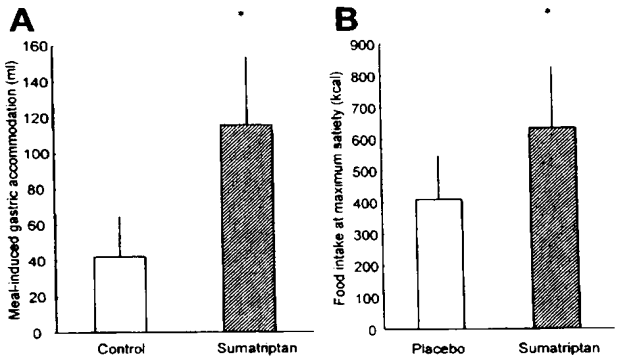

Figure 4. Influence of sumatriptan on postprandial gastric relaxation and on meal-induced satiety in patients with functional dyspepsia and impaired gastric accommodation to a meal. (*A*) Meal-induced gastric relaxation is expressed as the mean increase in intraballoon volume during 60 minutes after the meal, measured with a gastric barostat. In 6 patients, administration of 6 mg sumatriptan subcutaneously before the meal significantly increased the meal-induced gastric relaxation. (*B*) In 10 patients, preprandial administration of 6 mg sumatriptan subcutaneously significantly increased the amount of calories inducing maximum satiety.

of the gastric accommodation during the barostat study ($r = 0.47$; $P > 0.05$).

In patients, a significant correlation existed between satiety scores and the amount of calories ingested after placebo ($r = 0.61$; $P < 0.0001$). The amount of calories ingested at maximum satiety was only 450 ± 156 kcal ($P < 0.0001$ compared with healthy volunteers). A significant correlation existed between the amount of calories ingested during satiety testing and the amplitude of the gastric accommodation during barostat testing ($r = 0.66$; $P = 0.03$). Pretreatment with sumatriptan significantly enhanced the amount of calories ingested from 450 ± 156 to 671 ± 213 kcal ($P = 0.03$) (Figure 4*B*).

Discussion

Recent studies have reported impaired gastric accommodation to a meal in patients with functional dyspepsia.[9,10,13] The prevalence of impaired accommodation and its relevance and relationship to symptoms are unknown. We studied postprandial relaxation of the proximal stomach in 40 consecutive dyspeptic patients. We showed that impaired gastric accommodation is present in 40% of these patients. No correlation was present between defective postprandial relaxation of the proximal stomach and other pathophysiological mechanisms, such as the presence of *H. pylori* infection, delayed gastric emptying, or hypersensitivity to gastric distention. In univariate and multivariate analyses, impaired gastric accommodation was significantly associated with symptoms of early satiety. Weight loss was significantly associated with impaired gastric accommodation in univariate analysis but was not an independent factor in multivariate analysis. Therefore, weight loss is occurring secondary to early satiety: when early satiety is severe enough to interfere with adequate intake of calories, it leads to weight loss. The relation between impaired gastric accommodation and early satiety is also apparent from the correlation between the amplitude of the meal-induced relaxation and the amount of calories ingested at maximum satiety in patients with early satiety. Insufficient adaptive relaxation of the proximal stomach during and after the ingestion of a meal may be accompanied by activation of mechanoreceptors in the gastric wall, thus inducing symptoms.

This implies that restoring gastric accommodation should improve symptoms of early satiety. We showed that sumatriptan, a 5-HT_1 receptor agonist, enhances the meal-induced relaxation in patients with impaired gastric accommodation. Using a test to quantify meal-induced satiety, we showed that, in patients with early satiety, sumatriptan significantly enhanced the amount of calories ingested at maximum satiety.

The mechanism underlying impaired postprandial relaxation of the gastric fundus is unknown. Several possible pathways can be involved. Relaxation of the proximal stomach can be activated by duodenal distention or nutrient infusion via a vagal reflex pathway.[20,21] It requires activation of intrinsic nitrergic neurons in the stomach.[22] Theoretically, impaired relaxation can result from a disorder at the level of the sensory apparatus, vagal reflex pathway, or intrinsic inhibitory innervation. The presence of a relaxing effect of sumatriptan, which activates initrinsic inhibitory neurons,[23] suggests that gastric nitrergic neurons are functional in patients with an impaired gastric accommodation.

The current study has important implications for the treatment of patients with functional dyspepsia. So far, the pharmacological treatment of functional dyspepsia has relied on the use of prokinetic drugs. However, recent studies show that delayed gastric emptying is only present in a minority of dyspeptic patients,[14,16] and the reported therapeutic effects of prokinetics on symptoms are variable.[5,11,24-26] We showed that short-term administration of the fundus-relaxing drug sumatriptan is able to improve symptoms of early satiety that are associated with impaired gastric accommodation to a meal. Long-term studies with orally active fundus-relaxing drugs, such as buspirone or clonidine, seem warranted to confirm this therapeutic potential.[27,28]

In conclusion, our study showed that impaired gastric accommodation to a meal is present in a large proportion

of patients with functional dyspepsia. It is associated with symptoms of early satiety, which may lead to weight loss. The mechanism underlying impaired postprandial fundus relaxation is unclear, but it does not seem to involve *H. pylori* infection, visceral hypersensitivity, or delayed gastric emptying. Administration of the 5-HT_1 receptor agonist sumatriptan, a fundus-relaxing drug, improves early satiety in these patients. These observations confirm the therapeutic potential of fundus-relaxing drugs in functional dyspepsia patients with early satiety.

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Clinical Review

Triptans and gastric accommodation: pharmacological and therapeutic aspects

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Abstract

In the past decade, several studies have reported a significant delay of gastric emptying induced by the anti-migraine agent sumatriptan (a 5-hydroxytryptamine (5-HT)$_{1B/D}$ receptor agonist) in healthy human beings. In patients with functional dyspepsia, sumatriptan improves gastric accommodation after food consumption and reduce perception of gastric distension, hence relieving epigastric symptoms. Recent studies have established that impaired accommodation after food consumption is a major patho-physiological mechanism in functional dyspepsia and restoration of accommodation is considered to be a potential therapeutic target. The precise site of action of sumatriptan in humans is at present unknown, although recent studies carried out using a canine model indicate that sumatriptan exerts its action on gastric accommodation through 5-HT$_{1B}$ receptors, since both GR127935 and SB216641 (respectively, non selective 5-HT$_{1B/D}$ and selective 5-HT$_{1B}$ receptor antagonists) fully antagonised the effects of sumatriptan. Gastric relaxation and enhanced accommodation to a distending stimulus seem to be a class effect of triptans, since it occurs not only with sumatriptan, but also with second-generation triptans (rizatriptan and naratriptan), at least in a canine model. In dyspeptic patients, administration of triptans would be able to restore gastric accommodation after a meal and to improve symptoms of early satiety, confirming the therapeutic potential of 5-HT$_{1B/D}$ receptor agonists in functional dyspepsia.

Keywords: Dyspepsia; 5-HT Receptors; Gastric accommodation; Gastric motility; Triptans

1. Introduction

The term gastric accommodation describes the ability of the stomach to adapt itself following the ingestion of a meal. This response provides an appropriate gastric reservoir for food and enables volume increases without a rise in gastric pressure. It involves at least two responses: "receptive relaxation" [1], which allows the stomach to accept a load without a significant rise in gastric pressure, and "adaptive relaxation" [2], which modulates gastric tone in response to the specific properties of the food ingested. Normally, the proximal stomach relaxes in response to food ingestion in order to act as a reservoir and to enable an increase in gastric volume. Impaired gastric accommodation has recently been shown as a common finding in patients with functional dyspepsia [3,4]. Thus, restoration of gastric accommodation is proposed as a potential therapeutic target in dyspepsia [4].

The patho-physiological mechanisms responsible for functional dyspepsia include psycho-social factors and alterations in motility and visceral sensation. Approximately 50% of patients with functional dyspepsia have motor disorders, such as impaired fundic relaxation, antral dilation and/or hypomotility, small bowel dysmotility, or abnormal duodenogastric reflexes [5–8]. Tack et al. [9] have recently proposed the following relationship between gastric physiology and symptoms:

- delayed gastric emptying associated with post-prandial fullness, nausea and vomiting;
- impaired gastric (fundic) accommodation associated with early satiety and weight loss;
- visceral hypersensitivity associated with epigastric pain, belching and weight loss.

This classification, although simplistic, has the advantage of underlining the fact that subgroups of dyspeptic patients may considerably differ in the pathophysiology of their symptoms.

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In the past decade, many efforts have been made in order to extend our therapeutic armamentarium for dyspepsia, because the available drugs (mainly prokinetics) often do not provide adequate control of symptoms. Tack et al. [10] reported that, in healthy volunteers, sumatriptan, the anti-migraine agent caused significant relaxation of the gastric fundus and enabled the accommodation of considerably larger volumes before thresholds for perception or discomfort were reached during iso-volumetric distension. The fact that perception thresholds were altered by sumatriptan in response to iso-volumetric, not isobaric, distension suggests that the effect of sumatriptan was determined by the change in gastric tone rather than by an effect on visceral sensitivity. These observations provide a rationale for testing sumatriptan as means for relieving symptoms in dyspeptic patients with defective post-prandial gastric accommodation.

Different hypothesis have been put forward to explain the effect of sumatriptan. Recently, it was demonstrated that 5-hydroxytryptamine (5-HT)-induced relaxations of the guinea pig stomach are mediated through activation of a 5-HT_1-like receptor [11]. Some authors also considered 5-HT_{1P} receptors, since their presence is reported in enteric neurons [12], and suggested that sumatriptan might act via this receptor subtype [10] (see, however, Section 2).

The aim of the present review is to consider published evidence on the mechanisms involved in the action of triptans on gastric motility/visceral sensitivity, to consider possible new avenues for drug development for relieving symptoms in the subset of patients with functional dyspepsia and impaired gastric accommodation.

2. Role of 5-HT gastric accommodation

The presence of 5-HT was documented immuno-histochemically in the myenteric plexus of the stomach and there is enough evidence to support the hypothesis that 5-HT is a neurotransmitter in the enteric nervous system [13]. 5-HT is one of the neurotransmitters shown to be involved in vagally-mediated gastric relaxation [14,15]. The involvement of 5-HT receptors on intrinsic neurones in the vagally-mediated gastric relaxation in animals like the mouse and guinea pig has been demonstrated [16,17].

Although a number of 5-HT receptor agonists can alter gastric accommodation after food consumption [10,18,19], a physiological role for 5-HT in the control of proximal gastric tone in humans has not been established. The potential patho-physiogical targets and the effects of 5-HT receptor ligands are illustrated in Fig. 1. The main effects

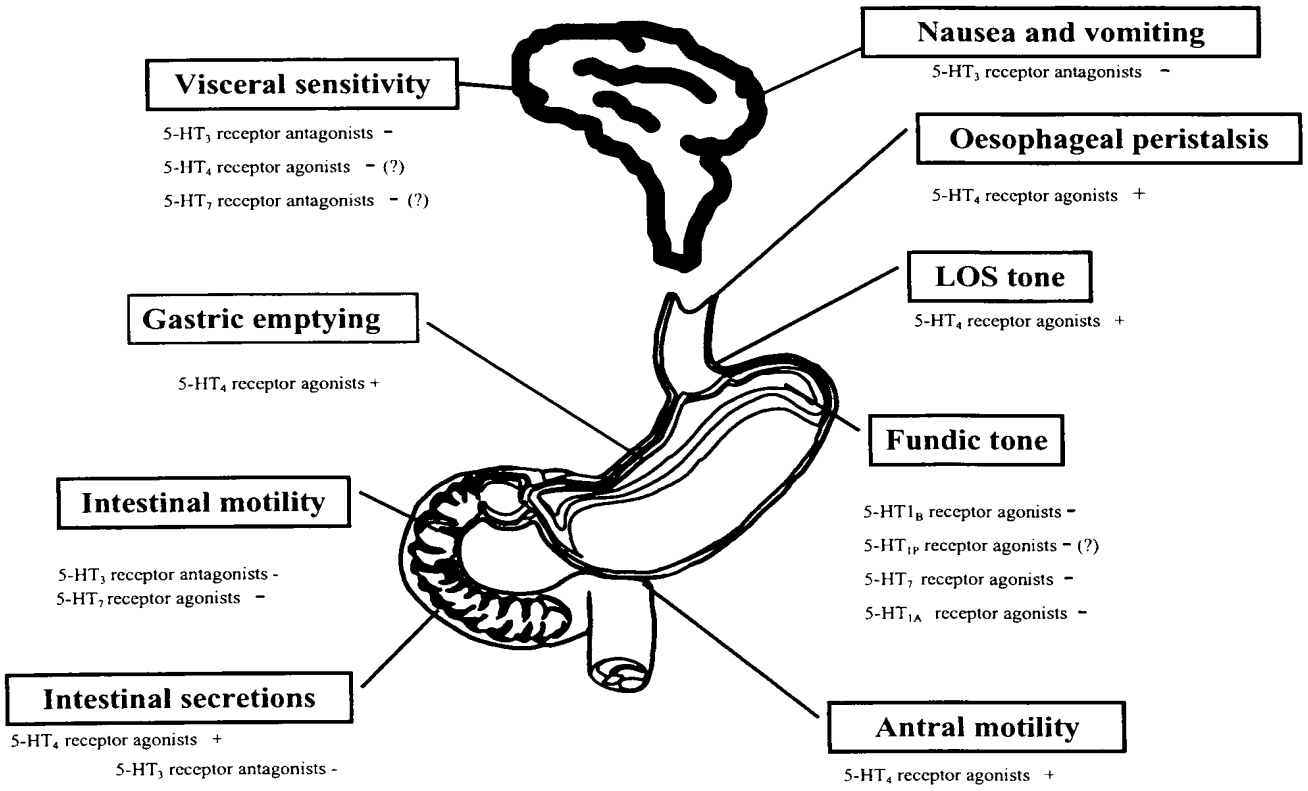

Fig. 1. Potential therapeutic targets in patients with functional disorders of the upper gut and effects of 5-HT receptor ligands. LOS = lower oesophageal sphincter; (+) indicates stimulation; (−) indicates inhibition. The reader is referred to the following publications [40,56,61–70].

relevant to gastrointestinal physiology seem to be mediated via 5-HT_{1A}, 5-$HT_{1B/D}$, 5-HT_3, 5-HT_4 and 5-HT_7 receptors. Because 5-HT is thought to be involved in vagally-mediated relaxation [14], several authors have investigated the effects of 5-HT re-uptake inhibitors that prolong the availability of physiologically released 5-HT, such as paroxetine [4,20], sertraline [21] and venlafaxine [20] on gastric sensory-motor function.

In particular, Tack et al. [4] reported that pre-treatment with oral paroxetine (20 mg daily for 7 days) had no influence on fasting gastric tone, fasting gastric compliance or the perception of gastric distensions in healthy volunteers studied with the help of a barostat. The authors suggested an effect of paroxetine on gastric accommodation after food consumption because of a significant difference in the post-prandial fundic relaxation between paroxetine and placebo. However, it should be noticed that the difference was small and that, in another study, [20] paroxetine did not have any effect on fasting or post-prandial gastric volume, measured using SPECT imaging of the stomach.

The role of 5-HT_3 receptors in the control of gastric emptying in humans was investigated using selective antagonists. One study reported enhanced gastric emptying of solids after administration of the 5-HT_3 receptor antagonist tropisetron [22], whereas other studies reported that the 5-HT_3 receptor antagonist ondansetron did not affect gastric emptying [23]. Moreover, ondansetron does not affect gastric fundic tone in humans, confirming that 5-HT_3 receptors are unlikely to be involved in the control of fundic tone [24,25]. Therefore, the observation that alosetron reduces postprandial symptoms in healthy subjects after ingestion of maximum tolerable volume of liquid food [26] is probably to be ascribed to an effect on visceral afferents rather than to increased post-prandial gastric volume.

In dogs, however, intravenously administered 5-HT induced contraction in the stomach, which was prevented by a 5-HT_4 receptor antagonist [27] and 5-HT_4 receptor agonists stimulate gastric emptying [28]. Recent in vitro and in vivo studies using a selective 5-HT_4 receptor agonist, prucalopride, confirmed the presence of 5-HT_4 receptors on cholinergic nerves in the canine gastric corpus [29]. Cisapride, a 5-HT_4 receptor agonist, was used as a prokinetic agent in dyspepsia [30]. The rationale for its use stood in its ability to enhance gastric emptying. Tack et al. [18] reported that, in healthy individuals, cisapride enhanced the perception of gastric distension an effect that theoretically should be detrimental in dyspeptic patients, but was not confirmed, in a different protocol, by Manes et al. [31]. However, cisapride can also enhance the gastric accommodation after food consumption [18] and reduce the average satiety scores [32] in healthy volunteers: these effects should turn out to be beneficial in dyspeptic patients with defective fundic accommodation. Indeed, studies carried out in guinea pigs have demonstrated that cisapride can also activate nitrergic inhibitory pathways in the stomach [33].

Different clues toward 5-HT_1 receptors mediating proximal gastric relaxation have been published. Moreover, it was demonstrated that 5-HT-induced relaxation of the stomach of the guinea pigs are mediated via the release of nitric oxide through activation of a 5-HT_1-like receptor [11,34] and Coulie et al. [35] using an in vivo cat model, suggested that sumatriptan (a 5-$HT_{1B/D}$ receptor agonist) can induce a relaxation of gastric fundus through activation of nitrergic pathways.

5-HT_{1P} and 5-HT_{1A} receptors have been identified in the myenteric plexus of the guinea pig stomach [36]. Tack et al. [10] ascribed the effect of sumatriptan to 5-HT_{1P} receptor agonism. However, it must be noticed that sumatriptan is the prototype 5-$HT_{1B/D}$ receptor agonist and that 5-HT_{1P} receptors are not included in the official IUPHAR classification of serotonin receptors [37] (see also Section 4, and [38]).

Concerning the 5-HT_{1A} receptors, Rouzade et al. [39] using flesinoxan (a 5-HT_{1A} receptor agonist), suggested that activation of these receptors at the level of the central nervous system can increase gastric tone and decrease gastric sensitivity to distension in rats. However, Xue et al. [40] have recently reported a peripheral inhibitory effect exerted by the 5-HT_{1A} receptor agonist buspirone on murine fundic tone. Interestingly, a preliminary account of a cross-over study of buspirone in patients with functional dyspepsia showed a reduction in symptoms and enhanced gastric accommodation after a meal [41].

3. Effects of sumatriptan in humans

In the past decade, several studies documented the effects of the 5-$HT_{1B/D}$ receptor agonist sumatriptan on gastric motility and sensitivity in the same dose-range used in migraine [42]. Houghton et al. [43] were the first to show that intravenous administration of sumatriptan in healthy subjects delayed gastric emptying of a nutritional liquid food. Subsequently, Coulie et al. [44] showed that sumatriptan in humans caused a notable delay in gastric emptying of both liquids and solids: of course, this effect is not desirable in those dyspeptic patients with already delayed gastric emptying. However, the same authors [10,44] also reported that sumatriptan also caused an immediate and profound relaxation of the gastric fundus in humans, thus enabling accommodation of considerably larger volumes before thresholds for perception or discomfort were reached during iso-volumetric distension.

Malatesta et al. [45] evaluated the effect of sumatriptan and of the anti-cholinergic hyoscine on gastric accommodation after liquid ingestion in normal subjects and dyspeptic patients. This study showed that, both in dyspeptic patients and in normal controls, gastric size measured after water distension was modified by sumatriptan, with a reduction in transverse and an increase in longitudinal size. Gastric distension with 500 ml of water induced the onset of nausea, bloating, heartburn, and to lesser extent, epigastric pain and,

as expected, the symptom score was higher in dyspeptics than controls. In this study, sumatriptan showed a beneficial effect only on the nausea induced by gastric distension both in dyspeptics and controls, without affecting the other symptoms.

In dyspeptic patients, the injection of subcutaneous sumatriptan was shown to restore gastric accommodation, improving the symptoms of early satiety [46]. Taking into account both the negative aspects (injections are expensive and inconvenient for the patients) and the positive aspect (intranasal sumatriptan is effective in curing migraine, with less adverse effects), Sarnelli et al. [47] tested the efficacy of intranasal formulation of the drug. In this study, the authors showed that intranasal sumatriptan was able to induce a significant increase in maximum balloon volume compared to placebo, but the effect was transient and no significant increase of the average gastric fundic volume 20 min after the drug administration was observed. Moreover, intranasal sumatriptan did not modify the sensations of perception and discomfort induced by gastric distensions and gastric compliance was not affected either. The negative results probably reflect a low bio-availability of the intranasal formulation.

Finally, because distension of the proximal stomach is a potent stimulus for the occurrence of transient lower oesophageal sphincter relaxation (TLOSRs, a major mechanism of reflux in patients with gastro-esophageal reflux disease and thus became an attractive target for pharmacotherapy [48], the effect of sumatriptan was also studied on the frequency of post-prandial TLOSRs and gastro-oesophageal reflux in healthy subjects [49]. Oesophageal manometry and pH monitoring were performed in 13 healthy volunteers for 30 min (before) and 90 min (after) a semi-liquid food (790 kcal). Sumatriptan 6 mg subcutaneously or placebo were administered on different days 30 min after food consumption. Sumatriptan significantly increased post-prandial LES pressure, but did not reduce the reflux events. On the contrary, reflux was more frequent after sumatriptan than after placebo. TLOSRs were more frequent after sumatriptan, particularly in the second 30 min period after drug administration. The authors conclude that sumatriptan prevents the natural decay in the rate of TLOSRs that occurs after food consumption and favours the occurrence of gastro-oesophageal reflux in spite of the increase in LOS pressure. The sustained post-prandial high rate of transient LES relaxation after sumatriptan may be a consequence of a prolonged fundic relaxation and retention of the food in the proximal stomach.

4. Effects of sumatriptan in animal models

Animal models have allowed us to gain more insight into the possible mechanism mediating the gastric-motor effects of sumatriptan. Coulie et al. [35], using an in vivo cat model, suggested that sumatriptan-induced relaxation occurs through activation of a nitrergic pathway. More recently, in a canine model, De Ponti et al. [38] showed that sumatriptan dose-dependence facilitated gastric accommodation to a distending stimulus in the 100–2400 nmol/kg intravenous dose range (i.e. approximately 0.5–16 times the subcutaneous dosage used for curing migraine): this action achieved statistical significance at the same dosage prescribed for migraine. By the use of selective antagonists (GR127935, SB216641 and BRL15572), 5-HT_{1B} receptors were shown to play an important role in mediating this effect [38]. Indeed, sumatriptan exerted its action on gastric accommodation through 5-HT_{1B} receptors, since both GR127935 (non selective 5-$HT_{1B/D}$ receptor antagonist) and SB216641 (selective 5-HT_{1B} receptor antagonist) fully reversed the gastric motors effect of sumatriptan, whereas the lack of effect of BRL15572 (selective 5-HT_{1D} receptor antagonist) suggests that 5-HT_{1D} receptors were not involved [38]. In the same study, sumatriptan induced a rapid-onset relaxation in a dosage of 400 and 800 nmol/kg administered intravenously. This response was short-lasting (usually <10 min) and baseline gastric volume invariably returned to the baseline within 15 min [38]. The gastric relaxation observed immediately after injection of sumatriptan can be prevented by SB216641, but not by BRL15572 (Fig. 2).

Several new triptans have recently become available for the treatment of migraine. This so-called "second generation" triptans include naratriptan, rizatriptan, eletriptan, zolmitriptan and frovatriptan. These compounds exhibit pharmacokinetic properties that may lead to a greater

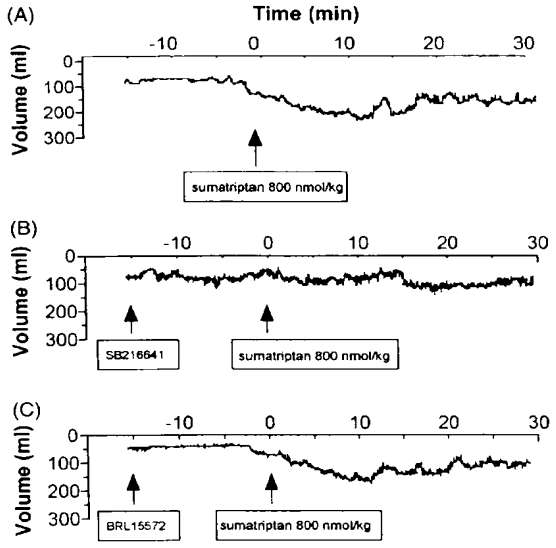

Fig. 2. Representative tracings of intra-gastric volume in the canine proximal stomach, measured using a barostat at a distending pressure of 2 mmHg, before and after intravenous administration of sumatriptan 800 nmol/kg alone (panel A) or combined with SB216641 (559 nmol/kg) (panel B) or BRL15572 (676 nmol/kg) (panel C). Note that sumatriptan causes an immediate volume increase reflecting fundic relaxation. Note that SB216641 totally prevents sumatriptan-induced relaxation. These experiments were performed in our laboratory according to methods described in detail in [38].

Table 1
Affinity values (expressed as p_{K_i}) of triptans at 5-HT receptor subtypes

Receptor subtypes	Sumatriptan [71–74]	Naratriptan [73,74]	Rizatriptan [71,73]
5-HT_{1A}	5.96 ± 0.06	7.12 ± 0.08	6.37 ± 0.04
5-HT_{1B}	7.37 ± 0.04	8.09 ± 0.07	6.86 ± 0.13
5-HT_{1D}	8.04 ± 0.02	8.41 ± 0.07	7.88 ± 0.07
5-HT_{1E}	5.79 ± 0.07	7.69 ± 0.04	6.77 ± 0.07
5-HT_{1F}	7.88 ± 0.06	8.18 ± 0.07	6.81 ± 0.06
5-HT_{2A}	<5.5	<5	<5.5
5-HT_{2B}	6.9	NA	6.6
5-HT_{2C}	<5.5	<5.5	<5.5
5-HT_3	<4	5.9	<5.5
5-HT_4	<5.5	<5	<5.5
5-HT_5	<5.5	5.47 ± 0.03	5.26 ± 0.03
5-HT_6	<5.5	<5.5	<5.5
5-HT_7	5.86 ± 0.11	<5.5	5.73 ± 0.13

therapeutic benefit than sumatriptan in some individuals. For example, they have higher bio-availability (40 to 75%), increased plasma half-life and shorter T_{max} [50]. From a pharmacological point of view, these agents are selective 5-$HT_{1B/D}$ receptor agonists and are similar to sumatriptan in that they do not allow any discrimination between 5-HT_{1B} and 5-HT_{1D} (see Table 1).

The ability to induce an immediate gastric relaxation and facilitate gastric accommodation to a distending stimulus is shared by second generation triptans. Naratriptan and rizatriptan also induce a rapid-onset relaxation at the dosage of 400 nmol/kg (Fig. 3), although to a different extent. As

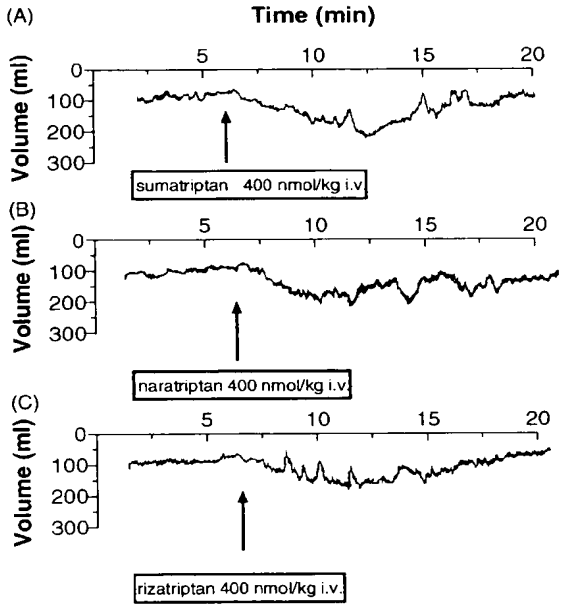

Fig. 3. Representative tracings of intra-gastric volume in the canine proximal stomach, measured using a barostat at a distending pressure of 2 mmHg, before and after intravenous administration of sumatriptan (panel A), naratriptan (panel B) and rizatriptan (panel C), all at the dosage of 400 nmol/kg. These experiments were performed in our laboratory according to methods described in detail in [38].

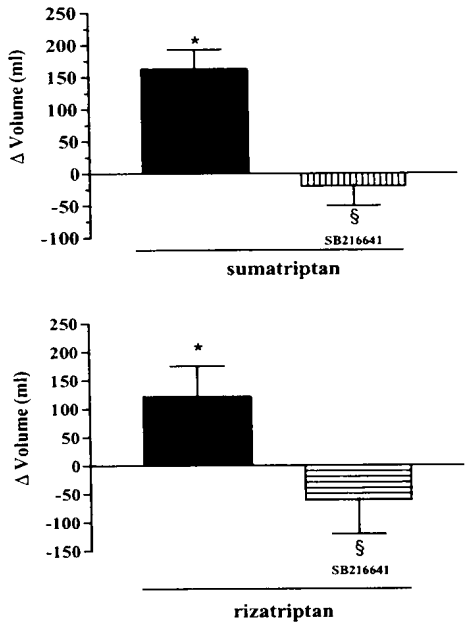

Fig. 4. Blockade of the effect of sumatriptan (800 nmol/kg) and rizatriptan (100 nmol/kg) by SB216641 in dogs. On the y-axis, Δ volume recorded at a distending pressure of 6 mmHg after sumatriptan and rizatriptan administration with respect to controls in the absence and presence of SB216641; (*) indicates $P < 0.05$ vs. control and (§) indicates $P < 0.05$ vs. triptan alone. Values are means ± SEM ($n = 4$). These experiments were performed in our laboratory according to methods described in detail in [38].

with sumatriptan, the increase in volume seen in rizatriptan (100 nmol/kg) was reversed by SB216641 (Fig. 4). Therefore, sumatriptan, and rizatriptan seem to have exerted their action through 5-HT_{1B} receptors, since SB216641 fully reversed the gastric motor effect of these triptans, at least in dogs.

In conclusion, gastric relaxation and enhanced accommodation to a distending stimulus seem to be a class effect of triptans, since it occurs not only with sumatriptan, but also with second-generation triptans (rizatriptan and naratriptan), at least in canine models.

5. Possible mechanisms underlying the gastric motor effect of triptans

The exact mechanism and site of action of sumatriptan is still unknown. The fact that sumatriptan poorly penetrates the blood-brain barrier [51–53] and also relaxes the stomach of the isolated guinea-pig [54] argues against an action at the level of the central nervous system. Indeed, several 5-HT receptor subtypes have been identified in the enteric nervous system and at the smooth muscle level (5-HT_1, 5-HT_2, 5-HT_3, 5-HT_4 and 5-HT_7) [55]. Selective antagonism of 5-HT_3 receptors did not influence inter-digestive and

post-prandial fundus tone in humans [25] and sumatriptan has little affinity at 5-HT_3 receptors (see Table 1).

Janssen et al. propose that the 5-HT_7 receptors may be involved in modulating relaxation of the proximal stomach in conscious dogs by a mechanism not involving NO [56,57]. Sumatriptan is unlikely to exert its action on gastric accommodation through 5-HT_7 receptors because the affinity value for this receptors is very low (see Table 1).

We should also consider 5-HT_{1P} receptors, since their presence is reported in enteric neurons [12], and some authors have suggested that sumatriptan might act via this receptor subtype [10]. However, 5-HT_{1P} receptors are not included in the official IUPHAR classification of serotonin receptors [37] and none of the authors reporting the gastric motor effects of sumatriptan in vivo has ever tested the effect of 5-HT_{1P} receptor antagonists because of the lack of selective agents suitable for in vivo use. The fact that the effect of sumatriptan was fully reversed by GR127935 and SB216641 supports the involvement of 5-HT_{1B} receptors.

6. Therapeutics perspectives

Recent studies showed that the accommodation of the gastric fundus to a meal is impaired in a subgroup of patients with functional dyspepsia and that this is associated with high prevalence of early satiety and weight loss [46].

Pharmacological interventions aimed at relaxing the proximal stomach may be effective in conditions characterised not only by impaired gastric accommodation but also by increased sensitivity to gastric distension, as seen for example in patients with functional dyspepsia.

So far, the pharmacological treatment of functional dyspepsia has relied on the use of prokinetic drugs. However, recent studies show that delayed gastric emptying is only present in a subset of dyspeptic patients [58] and that a significant proportion of these subjects display impaired fundic relaxation to a meal or an altered gastric sensitivity to distension [46]. In these patients, prokinetic drugs that contract the proximal stomach such as motilin receptor agonists are contraindicated [59,32], whereas a gastric relaxing drug such as sumatriptan could reduce early satiety [32]. Indeed, in patients with functional dyspepsia, hyoscine is reported to improve tolerance to gastric ballon distension [60]. In dyspeptic patients, administration of sumatriptan can restore gastric accommodation after food consumption and to improve symptoms of early satiety, confirming the therapeutic potential of 5-$HT_{1B/D}$ receptor agonists in functional dyspepsia. However, it should be noticed that at present there are no large-sample clinical trials with triptans and that recommendations for treatment are still based on empirical information obtained in the patho-physiological studies discussed in this review. Because the triptan-induced delay of gastric emptying may overcome the potential benefits associated with the documented increase in the accommodation response, it is important to identify those patients who are less likely to respond (i.e. those in whom symptoms are derived from delayed gastric emptying).

The available evidence warrants further studies to clarify the central or peripheral mechanism responsible for the gastric-motor effect of triptans and the effects on gastric motility/visceral sensitivity of second-generation triptans in humans. The use of selective 5-HT_{1B} receptor agonists endowed with gastrointestinal selectivity and limited potential to induce coronary vasoconstriction may open new avenues for the treatment of subsets of patients with functional dyspepsia.

Note added in proof

While this paper was in press, Janssen et al. [75] reported that flesinoxan induces gastric relaxation in conscious dogs via 5-HT_{1A} receptors and that this response is mediated through a non-nitrergic vagal pathway. Tack et al. [76] reported that, in healthy volunteers, tegaserod 6 mg b.d. enhances fasting gastric compliance and allows for larger intragastric volumes both before and after a meal.

Conflict of interest statement

None declared.

Acknowledgements

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T1307

Delayed Gastric Emptying in the Critically Ill: Correlation between Scintigraphy and Gastric Aspirate Volumes

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Gastric stasis is common in the critically ill and reduces tolerance to nasogastric feeding. Scintigraphy is rarely used in the critically ill for practical reasons. Volumes of gastric aspirates are frequently used as a surrogate marker of gastric emptying and to assess tolerance of enteral feeding. The purpose of this study was to establish gastric emptying rates in the critically ill and assess the relationship between gastric emptying measured by scintigraphy and volumes of gastric aspirates. The study was conducted in 17 unselected mechanically ventilated patients receiving enteral nutrition via a nasogastric tube and 8 normal volunteers. The scintigraphic measurement of gastric emptying involved a dynamic study performed in the ICU using a mobile gamma camera (GE Starcom) with the patient lying flat and the camera in the left anterior oblique position. Gastric emptying curves (expressed as % of the maximum content of the total stomach) were derived. The 50% emptying time and the retention at 240 minutes were documented. Data from patients were compared to volunteers and in the patients scintigraphic measurements of gastric emptying were compared to the gastric aspirate volumes. Results are expressed as median (IQR). There were 13 male patients and 6 male volunteers, the APACHE II score on the day of study was 16 (12-23), age 55 (45-68) in patients and 35 (22-57) volunteers. Gastric emptying was abnormal in 10 of the 17 patients. Gastric emptying was so delayed in 5 of the 17 patients that half-emptying time could not be calculated. Half emptying time ($n=12$) was 58 minutes (33-158). Normal half emptying time ($n=8$) was 57 minutes (31-75). Retention at 240 minutes ($n=17$) was 28% (1-68%) (normal 1%: $p=0.056$). Aspirate volumes were 70 ml (10-285). Retention at 240 minutes correlated with aspirate volumes ($r=0.76$, $p<0.01$). All patients continued to be fed despite poor gastric emptying (1600 ml/day (1020-1920)). Scintigraphy confirms that gastric emptying is severely delayed in some critically ill patients. Gastric emptying measured by scintigraphy correlates with gastric aspirate volumes. Enteral feeding may continue despite poor gastric emptying, however nutrient absorption is unknown.

T1308

Influence of Tegaserod on Proximal Gastric Sensory and Motor Function in Man.

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Background: Recent studies indicate that functional dyspepsia (FD) is a heterogeneous disorder, in which different pathophysiological disturbances are associated with specific symptom patterns. The main candidate mechanisms involved in FD symptom generation are delayed gastric emptying, hypersensitivity to distention and impaired accommodation to a meal. Tegaserod, a 5-HT_4 receptor partial agonist, enhances gastric emptying (1), suggesting therapeutic potential in FD, but its effects on proximal stomach function have not been studied. Aim: To study the effect of tegaserod on perception of gastric distention and on gastric compliance in man. Methods: Nineteen healthy volunteers (10 women, mean age 23.9 years) were studied on three separate occasions, each after 1 week washout and 7 days pretreatment, with either placebo (P), tegaserod 2 mg b.i.d. (T4) or tegaserod 6 mg b.i.d. (T12) in double-blind, randomized, cross-over design. After introduction of a gastric barostat bag, drug was administered. After 30 min., graded isobaric distentions (2 mmHg increments/2 min) were performed to determine gastric compliance and sensitivity to distention. Subsequently, the pressure level was set at intra-abdominal pressure (MDP) +2 mmHg for 90 min, with administration of a liquid meal (200 ml; 300 kcal) after 30 min. All data are given as mean ± SEM. Results: T12 showed a trend for enhancing fasting gastric compliance (P: 57 ± 4; T4: 58 ± 4; and T12: 67 ± 7 ml/mmHg, $p=0.09$ vs P). Pretreatment with tegaserod had no effect on pressures (P: 10.1 ± 0.8; T4: 10.9 ± 0.8; and T12: 10.1 ± 1.0 mmHg above MDP, NS), or volumes (P: 612 ± 44; T4: 666 ± 49; and T12: 674 ± 43 ml, NS), inducing discomfort. Both pre and post-meal, intra-balloon volumes at MDP + 2 were significantly higher after T12 (respectively P: 140 ± 18 and 288 ± 37; T4: 188 ± 24 and 349 ± 38, $p<0.1$ vs P; and T12: 201 ± 29 and 375 ± 41 ml, $p<0.05$ vs P). The amplitude of meal-induced gastric relaxation (post-meal minus pre-meal volumes) was not significantly altered (P: 148 ± 28; T4: 161 ± 27; and T12: 174 ± 32 ml, NS). Conclusion: In man, tegaserod allows larger intragastric volumes both before and after a meal. Thus, in addition to enhancing gastric emptying, tegaserod may also improve impaired accommodation, leading to a strong rationale for evaluation in FD. (1) Degen APT 2001

T1309

Transpyloric Flow of Low Calorie Liquid Meal Measured by Digitized Doppler Ultrasound

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Patterns of transpyloric flow can be studied by Doppler ultrasound. We have developed a software for digitizing the recorded Doppler data(LabVIEW 5.1, National Instruments). Aim: To investigate transpyloric flow during emptying of a low nutrient liquid by using digitized Doppler data. Methods: Ten healthy volunteers (5F) consumed 500ml of low calorie soup. Using 3.5mHz Doppler ultrasound, the transpyloric plane was imaged for 30 min in 10 min intervals to assess the pattern of transpyloric flow, divided into ante- and retrograde flow periods. The bi-directional sound information on the tape were transferred (using audio-out of the video recorder and audio-in on the audio card) to a computer and the digitized Doppler data were saved on disk. The software allowed information of both flow duration and flow velocity. The sum of emptying and reflux periods containing those data over time were used for analysis. Antral area, proximal stomach volume were assessed for each interval. Results: Both proximal stomach volume and antral area over time were significantly reduced ($p < 0.0001$ and $p < 0.001$, respectively). A positive correlation ($r = 0.83$, $p < 0.005$) was found between nett forward flow, calculated as Area Under the Curve (AUC) of the difference between AUC of forward flow and AUC of retrograde flow, and reduction of proximal stomach volume over time. No correlation was found between reduction in antral area and nett forward flow. Conclusion: The new developed software for digitizing ultrasound Doppler data can be used to study transpyloric flow using the information of both flow duration and flow velocity. The relationship between proximal stomach emptying and nett transpyloric forward flow supports the idea that the proximal stomach is assigned to control gastric emptying of liquids.

A5

T1310

A Novel Method to Measure the Gastric Emptying Using Magnetic Fluid

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BACKGROUND: Many methods have been established to evaluate gastric emptying (GE) either directly or indirectly. The isotope method is the one of the best precise way to measure GE, although it has a practical problem in deal with including radioexposure to patients. On the other hand, ^{13}C-breath test has been widely and quickly developed as a valuable indirect method for the measurement of GE, however this method is still indirect. An establishment of the direct method to measure GE without using radioisotope has been eagerly expected. AIM: To create a novel concept to measure GE directly using magnetic fluid, and to estimate its possibility for clinical use. METHOD: The principle of this new method is based on the two innovative works. The first is a development of water base magnetic fluids applicable to animals and human. Fine magnetite particle with an average size of 8nm was precipitated from $FeCl_2$, $FeCl_3$, and NaOH solution. Sodium oleic acid was absorbed as a first surfactant and several potential second surfactants were examined with reference to biocompatibility. The stability of these magnetic fluids was evaluated in both gastric and pancreatic juice corrected from dogs. Using these dogs, the levels of serum iron were measured after intragastric loading of these magnetic fluids. The second is a creation for evaluating system analyzed by a spatial integrated measurement for value of perturbation of magnetic fluid that is located in the uniform magnetic field generated by a Helmholtz coil. Magnetic flux was measured by using a flux gate type magneto sensor. During magnetic solution being allowed to flow out gradually from the model stomach of a canine, change of magnetic flux was detected. These data were spatially integrated to make a two-dimensional figure of model stomach, and the degradation of Hall voltage in center of each horizontal section filed was analyzed. RESULTS:1) The best biocompatible second surfactant was Rheodol TWO120 (mono oleic acid polyoxiethylene sorbitane)which is known as a safe for human. The magnetic fluid covered with this second surfactant was stable in both gastric and pancreatic juice, and did not show any increase of serum iron. 2) Not two-dimensional anterio-posterior but horizontal figure of model stomach was obtained by using the present measuring system. The degradation time of Hall voltage measured at the center of this figure was reflected to the GE of magnetic fluid from the model stomach. CNCLUSION:The present system is indicated as a new novel method for the direct measurement of GE without radioexposure.

T1311

Effects of Persistent Gastric Injury on Rat Spinal Afferent Neurons

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We have recently shown that acute gastric inflammation induced by acetic acid (HAc) injection into the gastric wall causes hyperalgesia and changes in the properties of voltage-sensitive sodium currents in rats. The present study examined whether voltage-sensitive currents were similarly affected 1 month after HAc injection. METHODS: To identify gastric sensory neurons, DiI was injected into the gastric wall of male rats. Seven days later, saline or HAc was injected into the dorsal and ventral glandular stomach during a laparotomy. The T9, T10 dorsal root ganglia were harvested one month later for cell dissociation. Patch clamp recordings were performed 2 to 6 h after dissociation. RESULTS: When cells were depolarized from -100 mV to 10 mV, there were no differences in peak inward (-10,077 ± 2127 vs. -9213 ± 1365 pA) or outward currents (9611 ± 1197 vs. 10131 ± 1136 pA). Based on their voltage-dependence of inactivation, we separated tetrodotoxin (TTX) sensitive (V1/2 = -57.3 ± 1.4 mV) from TTX resistant (V1/2 = -23.8 ± 1.6 mV) by holding cells at -30 mV. The peak inward current fell to about 50 % (-5392 ± 1933 pA) in control neurons and to about 20 % (-2259 ± 597 pA) in neurons from HAc-treated animals. CONCLUSION: Despite behavioral evidence of gastric hyperalgesia 1 month after HAc treatment (Ozaki et al.), we noted only minor changes in voltage-sensitive currents with a relative decrease in the contribution of TTX resistant sodium channels to the peak inward current. These results argue against a continuing contribution of peripheral mechanisms to gastric hyperalgesia, suggesting a role for central mechanisms.

T1312

Gastric Motor Function Assessment Using Capsules Containing Contrast Medium and Effects of Mosapride Citrate in Patients with Diabetic Gastropathy

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Objective: In recent years, our attention is now focused on diabetic gastropathy, one of the complications of diabetes. Although there have been many reports on gastric function, they have concentrated on gastric emptying and there have been no report from the view of intragastric distribution. In the present study, we used capsules containing contrast medium to investigate gastric emptying and intragastric distribution from changes in the number of capsules in the stomach in patients with diabetic gastropathy. We also examined changes caused by mosapride citrate. Methods: We studied 12 patients with poorly controlled type 2 diabetes (HbA1C 8.6+-0.9) in a diabetic group (DM), 19 normal individuals in a control group (CONTROL). We observed changes in the number of capsules remaining in the stomach and in distribution were examined under X-ray fluoroscopy at 0, 5, 15, 45, 60, 90, 120, 150 and 180 min. after oral administration of 15 capsules containing contrast medium and 200ml of Okunos-A as reported previously (.Dig Dis Sci. 1999 44:1741-6). Observations were made separately in the proximal stomach and distal stomach. Result: The total number of capsules emptied from the stomach was significantly lower in the DM than in the CONTROL ($p<0.0001$). In intragastric distribution, the number of capsules remaining in the proximal stomach

From Alimentary Pharmacology & Therapeutics

Influence of Tegaserod on Proximal Gastric Tone and on the Perception of Gastric Distension

Posted 01/12/2004

J. Tack; R. Vos; J. Janssens; J. Salter; S. Jauffret; G. Vandeplassche

Summary and Introduction

Summary

Background: Tegaserod, a 5-hydroxytryptamine-4 receptor agonist, enhances gastric emptying, but its effects on proximal stomach function have not been studied.
Aim: To study the effect of tegaserod on gastric compliance, accommodation and perception of distension in humans.
Methods: Nineteen healthy volunteers (10 females; mean age, 23.9 years) were studied on three separate occasions after 7 days of treatment with placebo, tegaserod 2 mg b.d. or tegaserod 6 mg b.d. in a double-blind, randomized, three-way cross-over design. After the introduction of a barostat bag, stepwise distensions were performed to determine gastric compliance and sensitivity, and a mixed liquid meal was administered in isobaric mode to assess accommodation.
Results: Tegaserod had no effect on the pressures or volumes inducing first perception or discomfort. Tegaserod 6 mg b.d. enhanced fasting gastric compliance compared with placebo. Pre-prandial and post-prandial intra-balloon volumes were significantly higher after 6 mg b.d. than after placebo. Both tegaserod 2 and 6 mg b.d. shortened the time to maximum post-prandial intra-balloon volume. The amplitude of meal-induced gastric relaxation (post-prandial minus pre-prandial volumes) did not differ between the treatment arms.
Conclusion: In humans, tegaserod allows for larger intra-balloon volumes both before and after a meal. These findings warrant the investigation of the therapeutic potential of tegaserod in dyspeptic patients with impaired accommodation.

Introduction

Dyspepsia is a clinical syndrome defined by chronic or recurrent upper abdominal symptoms without identifiable cause by conventional diagnostic means.[1] The symptom complex is often related to feeding and includes epigastric pain, bloating, early satiety, fullness, belching, nausea and vomiting.[1]

The pathophysiology of dyspepsia is not fully established, but a number of possible mechanisms have been suggested. Traditionally, delayed gastric emptying of solids and liquids was regarded as the principal cause of dyspepsia symptoms, but large studies have demonstrated that delayed emptying is present in only 20-35% of patients.[2-4] More recently, barostat studies of the proximal stomach have demonstrated hypersensitivity to gastric distension and impaired accommodation to a meal as possible pathophysiological abnormalities in dyspepsia.[5-10]

Tegaserod (3-(5-methoxy-1H-indol-3-ylmethylene)-*N*-pentyl-carbazimidamide hydrogen maleate), a selective 5-hydroxytryptamine-4 (5-HT_4) receptor partial agonist used in the treatment of patients suffering from irritable bowel syndrome with constipation,[11] is currently under evaluation for the treatment of dyspepsia. Tegaserod has been shown to enhance gastric emptying of solids in humans;[12] however, the effects of tegaserod on gastric accommodation to a meal and sensitivity to gastric distension have not yet been evaluated.

Section 1 of 4 Next Page: Materials and Methods

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1: Dig Dis Sci. 1998 Mar;43(3):491-6. SpringerLink FULL-TEXT ARTICLE Links

Proximal gastric motor activity in response to a liquid meal in type I diabetes mellitus with autonomic neuropathy.

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Disordered gastric emptying occurs in 30-50% of patients with diabetes mellitus. Although the rate of gastric emptying is dependent on the integration of motor activity in different regions of the stomach, there is limited

information about the function of the proximal stomach in diabetes mellitus. In the present study the response of the proximal stomach to a liquid meal was examined in eight diabetic patients with autonomic neuropathy and gastrointestinal symptoms and in 10 healthy volunteers, using an intragastric bag connected to an electronic barostat. Postprandial relaxation of the proximal stomach was measured as an increase of intragastric bag volume at a constant pressure level of 1 mm Hg above the intraabdominal pressure. During the experiment the blood glucose levels were maintained within the euglycemic range. Before ingestion of the meal the intragastric bag volume was larger in the diabetic patients than in the healthy volunteers, 234.4 +/- 29.1 ml vs 155.3 +/- 15.3 ml (P = 0.06). The maximum volume was not different in diabetics compared to the healthy controls (386.3 +/- 45.2 ml versus 399.0 +/- 35.2 ml). However, the maximum volume increase was significantly less in diabetics (143.7 +/- 38.6 ml) compared to the controls (231.4 +/- 30.5 ml, P < 0.04). Bloating was inversely correlated with the volume changes, which suggests that impaired relaxation of the proximal stomach may play a role in the genesis of this sensation. In conclusion, this study shows a lower fasting fundal tone and a decrease in volume change of the gastric fundus after a nutrient drink in patients with autonomic neuropathy due to type I diabetes mellitus. These abnormalities may play a role in the abnormal distribution of food, disordered liquid gastric emptying, and in the genesis of the sensation of bloating observed in these patients.

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Longterm oral cisapride improves interdigestive antroduodenal motility in dyspeptic patients

P A Testoni, F Bagnolo, L Fanti, S Passaretti, A Tittobello

Abstract

We have evaluated the effect of cisapride on interdigestive antroduodenal motility during a prolonged oral therapy in 20 consecutive dyspeptic subjects. Individuals with less than two migrating motor complexes (MMCs) starting from the antral region in 240 minutes and without evidence of upper gastrointestinal tract diseases were randomly treated with either cisapride (10 cases), or placebo (10 cases) for 15 days. Computerised manometry of antroduodenal region was performed for 240 minutes, in basal conditions and on the 15th day of therapy. Symptomatic evaluation of patients was also performed before and after treatment. After cisapride administration, a significant increase in the incidence of antral migrating motor complexes was noticed ($p=0.022$); likewise, the motility index, calculated for phase-2 periods, appeared to be significantly higher both in the antrum and in the duodenum ($p<0.001$). Symptomatic improvement was observed in both groups, with a hardly significant ($p=0.049$) reduction of dyspeptic symptoms severity only but not of frequency in cisapride treated patients *v* controls. We conclude that longterm oral therapy

In recent years, motor disorders of the antroduodenal region have been reported among the main factors involved in pathogenesis of dyspeptic syndrome.[1-4]

Previous manometric recording of antroduodenal motor activity[1-7] and isotopic techniques[1 6] showed that delayed gastric emptying and duodenogastric biliary reflux are the most common disorders associated with various and persistent conditions of discomfort of the upper digestive tract, in the absence of organic diseases, that represent the socalled 'functional dyspepsia'.

The prevalence of this common but ill understood entity has been calculated by Krag[8] to be 27% in western populations. Antroduodenal motor disorders - and specifically the delayed gastric emptying - have formed the basis for the use of several prokinetic drugs, stimulating gastroduodenal motor activity, in the treatment of functional, non-ulcer dyspepsia.

Cisapride, a new prokinetic drug devoid of antidopaminergic and direct cholinergic effect, has been recently reported to activate the migrating motor complex (MMC) in the fasting state[9] and to accelerate gastric emptying[10 11] after iv administration, both in animals and man, as well as to significantly improve dyspeptic symptoms[12] and gastric emptying[13] during oral chronic treatment.

At present, however, only few and non-controlled data are available as to the effectiveness of prolonged oral administration of the drug on the patterns of the antroduodenal interdigestive motility cycle (IDMC).[14]

The aim of this study was, therefore, to assess the effect of prolonged oral treatment with cisapride on the interdigestive motility in patients suffering from persistent dyspeptic symptoms associated with documented motor abnormalities of the antroduodenal region and without evidence of upper gastrointestinal tract organic diseases.

Methods

SUBJECTS

Twenty consecutive dyspeptic patients, nine men and 11 women, aged between 22 and 60 years (median age, 39) who at manometric examination of antroduodenal region showed less than two MMCs starting from the antrum in 240 minutes, were included in the study.

All subjects had suffered from dyspepsia for at least six months. Organic diseases of the upper digestive tract were ruled out by means of endoscopy, ultrasonography, abdominal plain x-ray film and appropriate biochemical tests; pregnant women and patients with a history of previous abdominal surgery, hepatic diseases with portal hypertension, alcohol consumption

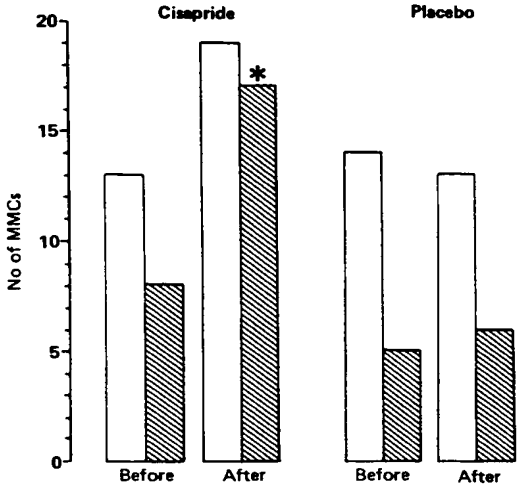

*Figure 1: Overall number of MMCs (open bars) and MMCs starting from the antrum (hatched bars), recorded before and after 15-day treatment with oral cisapride and placebo. Post-pretreatment comparison performed on single values by Wilcoxon's matched-pairs signed-rank test. *Statistically significant from baseline values, $p=0.022$.*

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exceeding 80 g/day and systemic diseases were also excluded. Informed consent was obtained from each subject admitted to the study.

EXPERIMENTAL DESIGN

All the patients entered a 15 day single blind randomised trial with either cisapride, 10 mg, orally administered four times daily, half an hour before each of the three main meals and at bed time (10 cases), or placebo (10 cases).

Manometric recording of interdigestive antroduodenal motor activity and symptom evaluation were performed in basal conditions and on the 15th day of treatment, the last tablet of the drug (cisapride or placebo) being administered in the fasting state half an hour before examination in order to evaluate the antroduodenal motility in steady state conditions. Over the trial duration, the patients were permitted to take only magnesium and aluminium hydroxide antacids, the consumption of which was monitored and compared.

MANOMETRIC RECORDING

After drugs affecting gastrointestinal motility and gastric secretion had been withdrawn for at least seven days, all patients underwent computerised manometric recording of the antroduodenal region. After an overnight fast, a five lumen polyvinyl chloride probe (external diameter, 0·5 cm) with five side holes spaced 5 cm apart and surface radiopaque markers located in the middle between the third and the fourth hole, was positioned under fluoroscopic control in the proximal part of the duodenum, by locating the radiopaque markers across the pyloric junction. The three upper recording holes were placed in the distal stomach (12·5, 7·5 and 2·5 cm before the pylorus) and the two distal holes in the proximal duodenum (2·5 and 7·5 cm after the pyloric ring). The probe position was also verified fluoroscopically at the end of the examination.

The recording catheters were perfused with distilled water, using a pneumohydraulic low compliance pump, and were connected by five Statham P23 ID transducers to a six channel polygraph (OTE Biomedica). Perfusion pressure was 50 kilopascal (375 mmHg) and perfusion rate was 0·5 ml/min. Respiratory excursions were monitored by means of a strain gauge pneumograph fitted around the patients' abdomen. Manometric data were collected and stored on disks for later analysis, by software developed in our centre. Recording of interdigestive motor activity was prolonged over 240 minutes, as suggested by other authors.[6 15-17]

According to previous reports,[15 18-20] the three different phases of each interdigestive motility cycle (IDMC) were visually identified: phase 1 characterised by motor quiescence, phase 2 by irregular motor activity, and phase 3, – that is, the migrating motor complex – by a short burst of rhythmic contractions (activity front).

The following determinants of the interdigestive motility cycle (IDMC) were evaluated: number and site of onset of migrating motor complexes (MMCs); duration of the IDMC; duration of each phase of the IDMC over the recording period. With regard to phase-2 periods, number and amplitude of phasic contractions were also determined, not including waves <8 mmHg to avoid erroneous evaluation of respiratory excursions. A motility index was also calculated, for each sequential 10 minute period and for each of the five recording channels, as number of waves × sum of amplitudes, according to the method described by Malagelada and Stanghellini.[4] The values thus computed were cumulated over time to obtain a phase-2 motility index per hour. Finally, phase-2 tracings were analysed for propagated motor waves – that is, contractions migrating aborally at 1–3 cm/sec and recorded consecutively at all the five recording channels.

SYMPTOM SCORING

The following nine symptoms, heartburn, regurgitation, belching, nausea, vomiting, postprandial fullness, postprandial drowsiness, epigastric pain, and bloating were recorded with regard to frequency (0=symptom absence; 1=one to three episodes/week; 2=four to seven episodes/week; 3=more than seven episodes week) and severity (1=mild; 2=moderate; 3=severe); the evaluation of symptom severity was formulated by the patients themselves, to avoid observer bias. Only subjects presenting at least three symptoms for over six months underwent manometric recording of interdigestive antroduodenal motility, in order to be included in the study.

STATISTICAL ANALYSIS

As the available data did not show a normal distribution or represented score values, statistical analysis was performed by means of non-parametric tests. After overall data were tested by Friedman's ANOVA, baseline values were confirmed to be comparable by Mann-Whitney U test; intraindividual changes (post-pretreatment) were evaluated using Wilcoxon's matched-pairs signed-rank test, two-tailed p values were computed.

TABLE 1 *Duration of the single phases of the IDMC over the recording time, number and duration of the IDMCs before and after 15-day treatment with oral cisapride and placebo*

		Phase 1 (min)	*Phase 2 (min)*	*Phase 3 (min)*	*IDMCs (n)*	*Duration of the IDMC (min)*
Cisapride	Baseline	134·5 (102–156)	102·5 (69–126)	8·0 (0–15)	4	132·5 (85–162)
	Post treatment	117·5 (98–151)	109·5 (60–134)	13·5 (3–29)	9	99·0 (56–126)
Placebo	Baseline	113·5 (105–143)	115·0 (91–132)	8·5 (0–18)	5	110·0 (84–154)
	Post treatment	119·0 (95–154)	114·5 (86–129)	7·5 (0–17)	5	136·0 (81–168)

Values are median and range. IDMC=interdigestive motility cycle.

TABLE II *Antral and duodenal phase-2 motor activity before and after 15 day treatment with oral cisapride and placebo*

		Phasic contractions			
		n/h		*Mean amplitude (mmHg)*	
		Antrum	*Duodenum*	*Antrum*	*Duodenum*
Cisapride	Baseline	52·0 (20–114)	94·5 (48–149)	24·95 (13·8–36·2)	21·10 (16·1–28·5)
	Post treatment	87·5 (56–155)*	116·0 (75–189)*	29·65 (17·5–37·1)†	23·50 (14·9–28·1)
Placebo	Baseline	61·0 (25–106)	92·5 (49–137)	23·50 (14·9–32·8)	20·30 (15·4–29·1)
	Post treatment	67·0 (35–109)	98·0 (60–134)	22·30 (15·4–31·2)	20·25 (15·5–27·4)

Values are median and range.
Significant at *p<0·001, †p=0·001 compared with baseline values.

Results

ANTRODUODENAL MOTOR ACTIVITY

Longterm treatment with oral cisapride appeared to significantly increase the number of MMCs starting from the gastric antrum (p=0·022) and consequently the overall number of activity fronts (Fig 1). In fact, at the admission to the trial and after the treatment with placebo no patient showed more than one antral MMC in 240 minutes, while on the 15th day of cisapride administration seven out of the 10 patients presented two or even three (one case) MMCs starting from the antrum in 240 minutes.

An increase in the number of complete IDMCs recorded (from the end of an activity front to the end of the successive one) was also observed, even if the small number of data do not allow a statistical evaluation (Table I). No differences were pointed out regarding the duration of the single phases of the IDMC.

Number and amplitude of phase-2 contractions and phase-2 motility index were evaluated by comparing the cumulated values of the three antral and of the two duodenal recording channels. The results (Table II) show in the cisapride treated patients a highly significant increase (p<0·001) of phase-2 motor waves frequency both in the antrum and in the duodenum; moreover, in the antral region a higher frequency correlated with a corresponding increased amplitude of phasic contractions (p=0·001).

As summarised in Figures 2 and 3, both antral and duodenal phase-2 motility index values (p<0·001) as well as the number of propagated waves per hour (p=0·005) also appeared significantly higher after cisapride administration, while they did not differ from baseline values after placebo.

SYMPTOM EVALUATION

In both the groups, no significant variation was detected in the number of symptoms which each patient complained of before and after the treatment. Symptom scores for frequency and severity of all the patients in basal conditions and during the 15 day treatment with oral cisapride or placebo are reported in Table III.

In comparison with pretrial values both cisapride and placebo significantly reduced overall symptoms frequency and severity, with cisapride superior to placebo (p=0·049) only in improving the severity of dyspeptic symptoms. As to discrete symptoms, no important variation was noticed in the two groups. No side effects were reported by the patients or detected by the physicians. Finally, no differences were observed between the two groups of treatment regarding magnesium and aluminium antacids consumption.

Discussion

Functional dyspepsia is a common event characterised by persistent or episodic symptoms

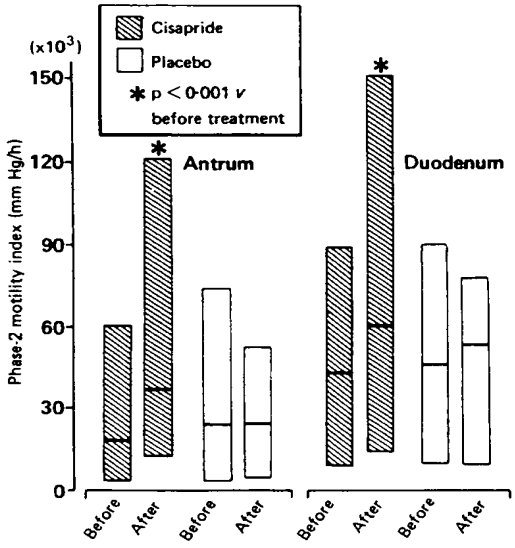

Figure 2: Antral and duodenal phase-2 motility index values (median and range), before and after 15 day treatment with oral cisapride and placebo.

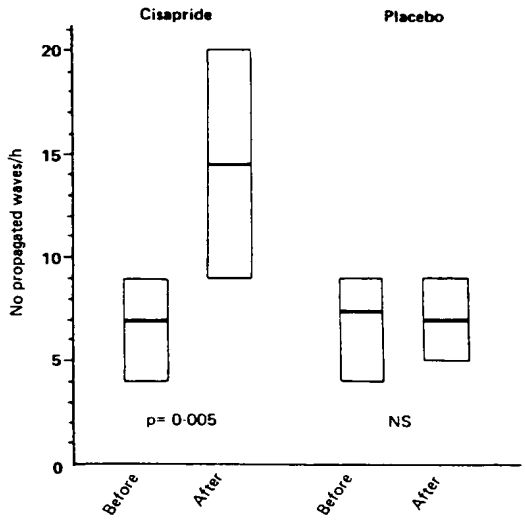

Figure 3: Number of propagated motor waves per hour (median and range), before and after 15 day treatment with oral cisapride and placebo.

TABLE III *Effect of 15-day treatment with oral cisapride or placebo on frequency and severity scores (median; extremes) of discrete and overall symptoms*

	Frequency				*Severity*			
	Cisapride		*Placebo*		*Cisapride*		*Placebo*	
	pre	*post*	*pre*	*post*	*pre*	*post*	*pre*	*post*
Heartburn	1; 1–3 (4)	0; 0–2 (1)	2; 2–2 (2)	0·5; 0–1 (1)	1; 1–2 (4)	0; 0–1 (1)	2·5; 2–3 (2)	1·5; 0–3 (1)
Regurgitation	3; 1–3 (8)	1; 0–3 (5)	3; 3–3 (5)	3; 2–3 (5)	2; 1–3 (8)	1; 0–2 (5)	2; 1–2 (5)	2; 1–2 (5)
Belching	3; 3–3 (2)	2; 2–2 (2)	3; 3–3 (5)	2; 2–3 (6)	3; 3–3 (2)	2; 2–2 (2)	2; 1–3 (5)	1; 1–3 (5)
Nausea	1·5; 1–2 (4)	1; 0–1 (3)	2; 1–3 (6)	1; 1–2 (6)	2·5; 2–3 (4)	1; 1–3 (3)	3; 1–3 (6)	2; 1–3 (6)
Vomiting	1·5; 1–2 (2)	0; 0–0 (0)	1; 1–1 (2)	0; 0–0 (0)	3; 3–3 (2)	0; 0–0 (0)	2; 2–2 (2)	0; 0–0 (0)
Postprandial fullness	3; 2–3 (7)	3; 2–3 (7)	3; 3–3 (8)	3; 3–3 (8)	3; 2–3 (7)	2; 1–3 (7)	3; 2–3 (8)	3; 2–3 (8)
Postprandial drowsiness	3; 3–3 (10)	3; 0–3 (9)	3; 3–3 (9)	3; 3–3 (9)	3; 2–3 (10)	2; 0–3 (9)	3; 2–3 (9)	2; 2–3 (9)
Epigastric pain	2; 2–2 (1)	0; 0–0 (0)	3; 3–3 (1)	2; 2–2 (1)	3; 3–3 (1)	0; 0–0 (0)	3; 3–3 (1)	1; 1–1 (1)
Bloating	2·5; 1–3 (4)	2; 1–3 (4)	3; 0–3 (5)	2·5; 2–3 (6)	3; 3–3 (4)	3; 3–3 (4)	2·5; 0–3 (5)	3; 1–3 (6)
Overall symptoms	10·5; 7–16	6·5; 1–12*	12; 8–17	10; 8–15*	10·5; 8–16	7; 1–11†	11; 7–16	9·5; 7–12*
			ns				p=0·049	

(n)=number of patients presenting the symptom.
Significant at *p=0·022, †p=0·014 compared with baseline values.

related to the upper digestive tract in the absence of organic diseases, occurring both in the fasting state and in the postprandial period. Previous studies suggest that major dyspeptic complaints, as nausea, bile vomiting, heartburn and regurgitation (occurring in the fasting state) or postprandial fullness and drowsiness or bloating (in the fed state) are likely to be dependent on motor abnormalities of the antroduodenal region, well documented by manometric recordings and isotopic techniques.[1–4] In fact, the prolonged duration of the interdigestive motility cycle associated with abnormalities in the frequency, onset and propagation of the migrating motor complex, has been shown to be related on the one hand to increased duodenogastric bile reflux, with possible impairment of the clearing capacity of the distal stomach and subsequent bile stasis in the fasting state,[7 18 21] and on the other hand to delayed gastric emptying.[6] The reduced incidence or the absence of MMCs in the antrum, regardless to any other parameter, particularly seems '*per se*' to play a major role in the dyspeptic syndrome.[4 6]

The significance of these abnormalities of the phase 3 of the IDMC in the antral region is at present unknown; it is also difficult to define a standard motility pattern in man, as a great variability in the incidence of migrating motor complexes has been reported both in healthy individuals and in dyspeptic subjects. Moreover, the multilumen probe inserted across the pylorus in the duodenum might be responsible for possible changes of antroduodenal motility, even if there is evidence that the catheter does not significantly affect the motility pattern.[21 22]

There is, however, general agreement that most normal subjects show at least two consecutive MMCs during a recording period of 240 minutes,[6 15 23] although in some cases the absence of MMCs has been described.[21] In the last years several reports have shown that cisapride is effective in the treatment of functional, non-ulcer dyspepsia, by improving both the antroduodenal motility pattern and the subjective symptoms.[10–13] Manometric recordings of the upper digestive tract motility have documented that iv infusion or single oral administration of cisapride during the phase 1 of the interdigestive motility cycle (IDMC) induces a prolonged and highly propagative phase-2 like jejunal motor activity in fasting humans[16 24] and improves the antroduodenal coordination.[25] Moreover, isotopic studies have shown that iv administration of the drug significantly accelerates gastric emptying of solids in dyspeptic subjects[10 11] and increases antral contraction amplitude in subjects with primary anorexia nervosa.[11]

In a preliminary non-controlled study after oral prolonged administration, cisapride seems to significantly accelerate gastric emptying[13] and improve the interdigestive motility cycle.[14] On the other hand, no objective data are at present available on the possible effectiveness of an oral prolonged treatment with cisapride in normalising the frequency of antral migrating motor complexes and in modifying other parameters of interdigestive phasic activity in patients suffering from non-ulcer dyspepsia.

Cisapride, orally administered for 15 days, appeared in our single blind placebo controlled study to be significantly effective in improving interdigestive antroduodenal motility. Cisapride particularly promoted a significant increase of MMCs starting from the gastric antrum; in fact, after the treatment with the drug seven of the 10 patients (*v* no case in the placebo group) showed two consecutive antral MMCs during the 240 minute recording period and they did not present any more the motor abnormalities required for inclusion in the study. Nevertheless, as regards dyspeptic symptoms, a similar improvement was observed in both the groups of treatment (cisapride was significantly more effective than placebo only in reducing symptom severity), without any correlation with antroduodenal motility pattern. This is not surprising considering on the one hand the role played by the placebo effect on the subjective evaluation of symptoms in dyspeptic patients and on the other hand the relatively short period of treatment. Also the fact that symptoms improved with the placebo despite any improvement in interdigestive antroduodenal motor activity suggest that motility disorders are not the only factor involved in the genesis of dyspepsia.

Partially in agreement with other studies performed with single doses of cisapride,[11 16 24] in our series the drug was shown to induce a phase-2 motor activity characterised by a significantly higher number and amplitude (this latter only in the antrum) of phasic contractions and by significantly more aborally propagated waves; on the other hand, we observed neither a pro-

longation of the time spent in the phase 2 of the IDMC, nor an increased interval between consecutive MMCs.

The improvement of the antroduodenal coordination, expressed by the increase of propagated waves, and the higher pressure activity recorded in the antrum but not in the duodenum, could be responsible for the acceleration of gastric emptying as pointed out by other authors,[10 11 13] after cisapride administration.

Further investigation would be probably required to verify these findings during the postprandial period also, by means of a 24 hour computerised manometric recording, thus comparing manometric and isotopic results.

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Effect of Cisapride and Renzapride on Gastrointestinal Motility and Plasma Motilin Concentration in Dogs

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ABSTRACT

The effects of cisapride and renzapride (BRL 24924), on plasma concentration of motilin and gastroduodenal motility were studied in seven dogs with implanted force transducers in the antrum and duodenum. In the interdigestive state, the i.v. administration of cisapride (5 mg) or renzapride (5 mg) administered in phase I resulted in a prompt and marked increase in plasma motilin concentration and in gastroduodenal motility. Mean plasma motilin levels during the first 30 min after cisapride and after renzapride injection were 85.0 ± 6.5 (± S.E.) and 96.1 ± 6.3 pM., respectively. These values were significantly greater ($P < .001$) than those for the corresponding time period of the control cycle, 52.2 ± 5.6 and 57.4 ± 5.3 pM (mean phase III level, 120 ± 8.1 pM), respectively. The increases in the motilin level after cisapride or renzapride coincided with significant increases in contractile activities of the antrum to 43.2 ± 5.3% and 44.9 ± 4.6% and of the duodenum to 28.4 ± 3.1% and 34.2 ± 2.2% of phase III activity (100%) from that in the corresponding control period, 0.7 ± 0.4% and 0.2 ± 0.1%, respectively. The changes in both plasma motilin and motility in response to the two drugs were abolished completely by the i.v. administration of atropine. The drugs also enhanced the meal-induced contractile activities of the antrum as well as the duodenum but failed to influence the postprandial plasma motilin concentration. We conclude that cisapride and renzapride have similar effects on plasma motilin and gastroduodenal motility: 1) the two drugs increase plasma motilin levels and stimulate gastroduodenal motility in the interdigestive state, and 2) in the digestive state, both drugs enhance motility without influencing the plasma motilin levels.

Cisapride is a prokinetic drug that is derived from a benzamide compound and is reported to be effective in the treatment of some gastric, small intestinal and colonic motor disturbances (Champion, 1989; Krevsky *et al.*, 1989; Lee *et al.*, 1984; McHugh *et al.*, 1992). In conscious dogs, the i.v. administration of cisapride stimulated digestive and interdigestive GI motility (Edwards *et al.*, 1987; Muller-Lissner *et al.*, 1986; Gullikson *et al.*, 1993; Schuurkes *et al.*, 1984). The mechanism of this action is not clearly known, although it has been suggested that it facilitates ACh release from the myenteric plexus (Van Nueten *et al.*, 1984). Previously, we reported that i.v. cisapride increased GI motility *via* an atropine-sensitive mechanism (Lee *et al.*, 1984).

A new substituted benzamide compound, renzapride (BRL 24924), which does not have any dopamine blocking activity, has also been reported to stimulate gastric motility (Bermudez *et al.*, 1990; Cooper *et al.*, 1986; Gullikson *et al.*, 1991; Gullikson *et al.*, 1993). It was reported that both cisapride and renzapride enhanced the contractions of the electrically stimulated ileum, but not contractions caused by exogenous ACh and therefore it was suggested that the action of both compounds was due to a stimulation of cholinergic neurons (Craig and Clark, 1990). Recently, it has been proposed that these two benzamide compounds exert their motility-stimulating actions *via* serotonin receptor (Gullikson *et al.*, 1993; Meulemans and Schuurkes, 1992) by activating serotonin-4 receptors (Ford and Clarke, 1993). In the present study, we have investigated the effect of both cisapride and renzapride on the plasma motilin concentrations and gastroduodenal motility in fasting and postprandial states.

Materials and Methods

Seven dogs (body weight 15 to 22 kg) were prepared with gastric cannulas and a set of three strain gauges sutured on the serosal walls of the antrum: two 4 cm and 2 cm proximal to the pylorus and one on the duodenal wall, 5 cm from the pylorus. Experiments were started at least 2 weeks after surgery. After an 18-hr fast, dogs were placed on the Pavlov stand, and the motility was recorded by using a Grass polygraph (Model 7PI). During the experiments, venous blood samples were obtained *via* an indwelling catheter in a vein of one of a fore or hind leg while the stomach cannula was left open to drain gastric juice. The stomach cannula was closed before a meal was fed.

Study design. Three different groups of studies were carried out.

1) **Interdigestive state:** at least two cycles of interdigestive motor activity, including phases I, II, III and IV were recorded before drug was administered. Phase I represents a quiescent period with no contractions that lasts about 30 to 60 min, phase II represents a period of random contractions that lasts about 20 to

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60 min and phase III represents a period of maximum contractions that lasts about 5 to 20 min and migrates aborally. Phase IV represents a transitional period between phase III and phase I, exhibiting random contractions similar to the phase II period and lasting 5 to 10 min. One cycle of the interdigestive motor activity lasts about 90 to 120 min in dogs (Code and Marlett, 1975). Cisapride or renzapride was administered i.v. in a bolus at a dose of 5 mg in phase I (30 min after the second phase III), and motility recording was continued for at least 2 hr more after drug administration. After i.v. administration of cisapride or renzapride, sampling of blood was made at intervals of 5 min during first 30 min and at intervals of 10 min thereafter. For the control, blood samples were obtained during the corresponding time period of the control cycle.

2) **Atropine background:** similar experiments were repeated under the influence of atropine sulfate at 5 μg/kg given i.v., followed by continuous infusion at 20 μg/kg/kg. Atropine was started at least 20 min before a testing drug was administered.
3) **Digestive state:** 30 min after the end of duodenal phase III, dogs ate a standard meal containing 150 g of cooked ground beef, 100 ml of milk and one slice of white bread. A testing drug was given i.v. 30 min after the meal. Blood samples were obtained at 5-min intervals for 30 min. The blood samples collected in heparinized tubes were placed immediately in ice, and at the end of the experiment, plasma was separated by refrigerated centrifugation at 3000 rpm for 10 min. Plasma samples containing 1 mM ethylenediamine tetra-acetic acid, 1.5 mg/ml of bovine trypsin inhibitor, 100 mg/ml of soybean trypsin inhibitor and 9.9×10^{-9}M D-Phe-L-Arg-CH_2Cl_2, a potent, specific, irreversible inhibitor of kallikreins were kept frozen at −20°C for future radioimmunoassay of motilin (Tai and Chey, 1978). Cisapride was supplied by Janssen Research Foundation, Piscataway, NJ, and renzapride by Beecham Pharmaceuticals, Surrey, England.

Measurement of plasma motilin and motility analysis. The plasma motilin concentration was determined at 5 to 10-min intervals, and gastroduodenal contraction was analyzed at 10-min intervals. The results of motility changes observed during first 30 min were expressed as percent contraction of phase III, during which maximum contractions (100%) occurred. In order to evaluate the effect of drug on motilin release and gastroduodenal contractile activity, the mean plasma motilin concentrations we determined and the contractile activity analyzed for 30 min after drug administrations were compared with those during the corresponding time period of the control cycle. Because the actions of both drugs were immediate, the initial effect was probably due to the direct action of either drug.

Analysis of data. The results were expressed as means ± S.E., and a linear model was used for comparison (Neter *et al.*, 1985). P values of less than .05 were considered statistically significant.

Results

During the interdigestive state, the i.v. administration of cisapride or renzapride resulted in prompt and marked increases in contractile activities of the antrum and duodenum (fig. 1). Mean contractile activities of the antrum and duodenum during the first 30 min after cisapride or renzapride administration were 43.2 ± 5.3 or 44.9 ± 4.6% and 28.4 ± 3.1% or 34.2 ± 2.2% of phase III contractile activity, respectively, values that were significantly higher ($P < .001$) than those of the corresponding control period, 0.7 ± 0.4% and 0.2 ± 0.1% (fig. 2). The contractile activity lasted for more than 2 hr—as long as the recording continued. The increase in the motility coincided with significant increases in plasma motilin levels from 52.2 ± 5.6 pM to 85.9 ± 6.5 pM after

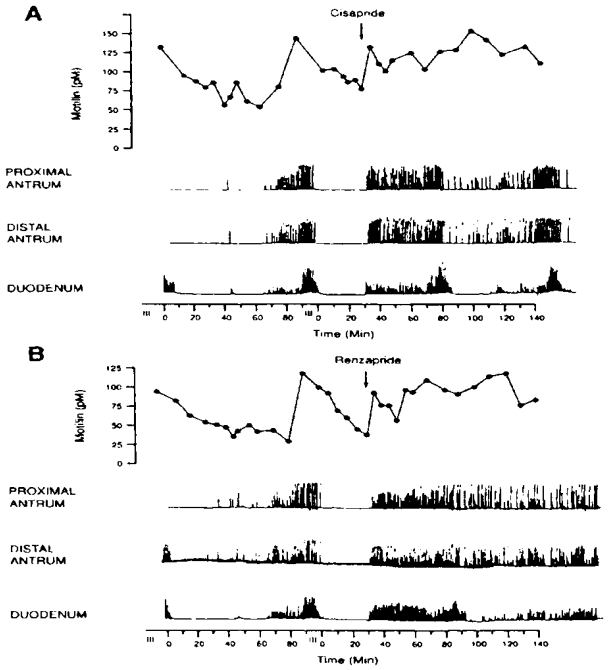

Fig. 1. Plasma motilin concentration (●—●) and the interdigestive motility of the gastric antrum and duodenum of one dog obtained before and after i.v. injection of cisapride (panel A) or renzapride (panel B). Arrow (↓) indicates the time when cisapride or renzapride was administered at dose of 5 mg i.v. bolus. A marked increase in motility was observed that coincided with the increase in plasma motilin concentration in response to cisapride or renzapride.

cisapride and from 57.4 ± 5.3 pM to 96.1 ± 6.3 pM after renzapride, respectively ($P < .01$) (fig. 2).

The increased motility induced by either cisapride or renzapride was completely suppressed by atropine. Also, the increase in plasma motilin concentration was completely abolished by atropine pretreatment (fig. 3).

A meal ingestion converted the motility to a digestive pattern immediately, which was enhanced by the i.v. administration of cisapride or renzapride (fig. 4). After cisapride, the increased motility after a meal, 12.5 ± 3.2% and 11.1 ± 4.2% observed in the antrum and duodenum, respectively, was enhanced further to 46.4 ± 3.0% and 24.8 ± 6.0% of phase III, respectively ($P < .01$). Similarly, renzapride significantly augmented ($P < .01$) the digestive motility from 12.3 ± 3.2% and 13.1 ± 3.5% to 41.6 ± 4.0% and 26.5 ± 5.0% of phase III in the antrum and duodenum, respectively (fig. 5). However, the drugs failed to influence the plasma motilin concentration (fig. 5). Mean postprandial plasma motilin levels during the first 30 min after cisapride and renzapride injections were 73.1 ± 4.2 pM and 70.9 ± 3.6 pM, respectively, values that were no different from those—76.4 ± 4.8 pM and 69.6 ± 3.4 pM, respectively—during the 30-min period before the administration of either of the two drugs.

Discussion

In the present study, we observed a significant increase in gastroduodenal motility when cisapride or renzapride was administered i.v., a result that confirms the previous publi-

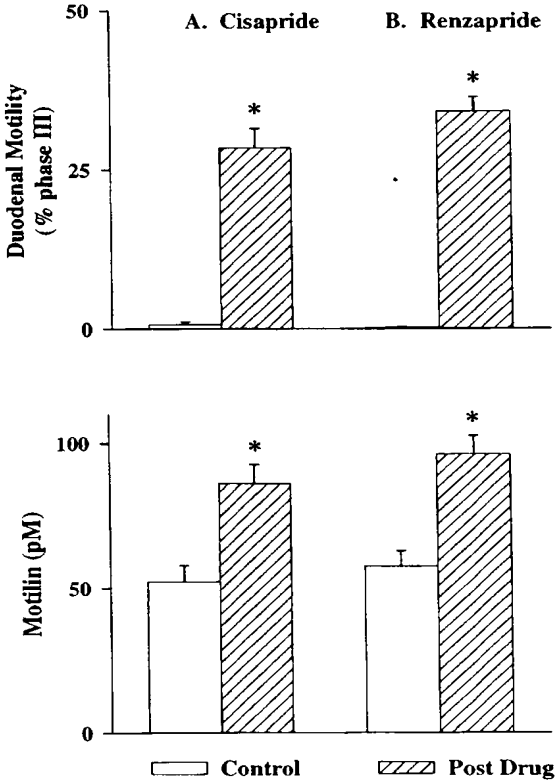

Fig. 2. Mean changes in duodenal motility and plasma motilin concentration in response to i.v. cisapride (panel A) or renzapride (panel B) in interdigestive states. A significant increase in motility and plasma motilin concentration was observed after i.v. cisapride (panel A) or renzapride (panel B), compared with those during the corresponding control period. *P < .01 to .001.

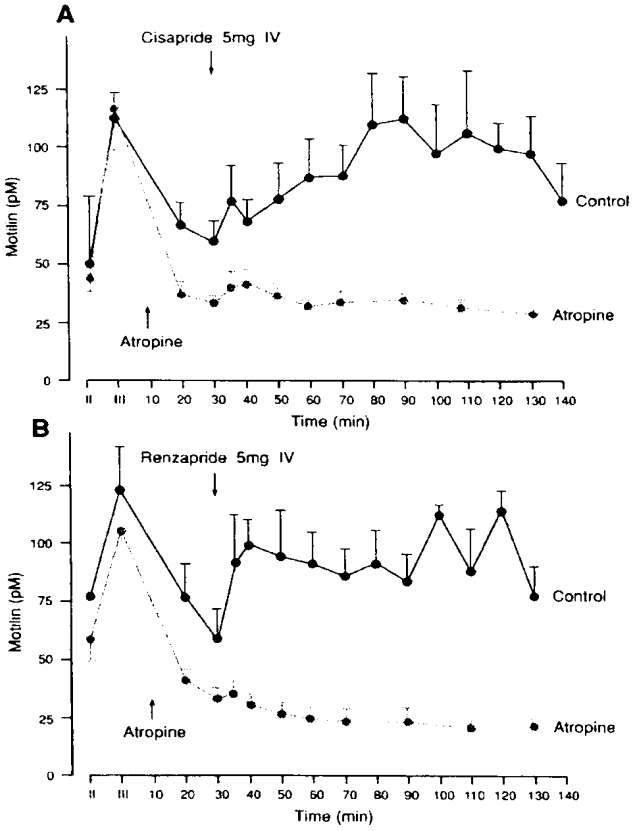

Fig. 3. Mean plasma motilin concentration in response to i.v. cisapride (panel A) or renzapride (panel B) with (⊛—⊛) or without (●—●) atropine background (5 μg/kg/h followed by 20 μg/kg/h i.v.). Atropine virtually abolished the increase in plasma motilin concentration.

cations (Bermudez *et al.*, 1990; Cooper *et al.*, 1986; Fraser *et al.*, 1993; Gullikson *et al.*, 1993; Sanger, 1987). In addition, significant increases in the plasma motilin concentration were observed after cisapride or renzapride administration. Thus we confirmed our previous observation that cisapride increased plasma motilin levels (Lee and Chey, 1984), although others failed to observe any changes in plasma motilin level (Kawagishi *et al.*, 1993; Suzuki *et al.*, 1984). The reason for this discrepancy between our observations and those of others is not known.

It has been previously shown that there is an intimate relationship between cyclic increase in fasting plasma motilin concentration and the interdigestive motor complex of the antrum and proximal small intestine (Chey *et al.*, 1978; Itoh *et al.*, 1978; Lee *et al.*, 1978). The increases in both plasma motilin level and contractile activity of the antrum and duodenum induced by cisapride or renzapride were almost completely blocked after atropine infusion, which suggests that the actions of these two drugs on the release of motilin and on the motility are mediated by local release of ACh (Craig and Clarke, 1990; Kilbinger *et al.*, 1995). A similar observation was made in the interdigestive state in dogs as well as humans (You *et al.*, 1980) in which cyclic increases in plasma motilin concentration coinciding with phase III motor activity of the duodenum were completely abolished by i.v. atropine (Chey *et al.*, 1978; Lee *et al.*, 1983).

In the postprandial state, neither of the two drugs raised the plasma concentration of motilin, although both significantly increased gastroduodenal motility. As shown previously, the cyclic increase in plasma motilin is interrupted by ingestion of a meal in dogs (Chung *et al.*, 1992; Lee *et al.*, 1980). The elevation of motilin may be suppressed during the postprandial period by increased releases of gut and pancreatic hormones such as pancreatic polypeptide (Adrian *et al.*, 1980; Hall *et al.*, 1983), insulin (Jenssen *et al.*, 1984) and somatostatin (Poitras *et al.*, 1980), which are known to suppress motilin release. In duodenectomized dogs, cyclic patterns of motility were preserved without any motilin fluctuations (Malfertheiner *et al.*, 1989), which suggests that a factor or factors in the duodenum contribute to the cyclic coupling of motility and motilin. More recently, Chung *et al.* (1992) reported that postprandial patterns of motility and motilin was converted to the fasting patterns when vagal tone was blocked by cooling. Thus in dogs, dissociation between the increase in plasma motilin and gastroduodenal motility in the postprandial state could be mediated by multiple factors, including hormonal as well as neuronal factors. Further studies will be needed.

Although the mechanisms of the action of cisapride and renzapride have not been clearly defined, it has been implicated that cisapride may act on motility by facilitating the

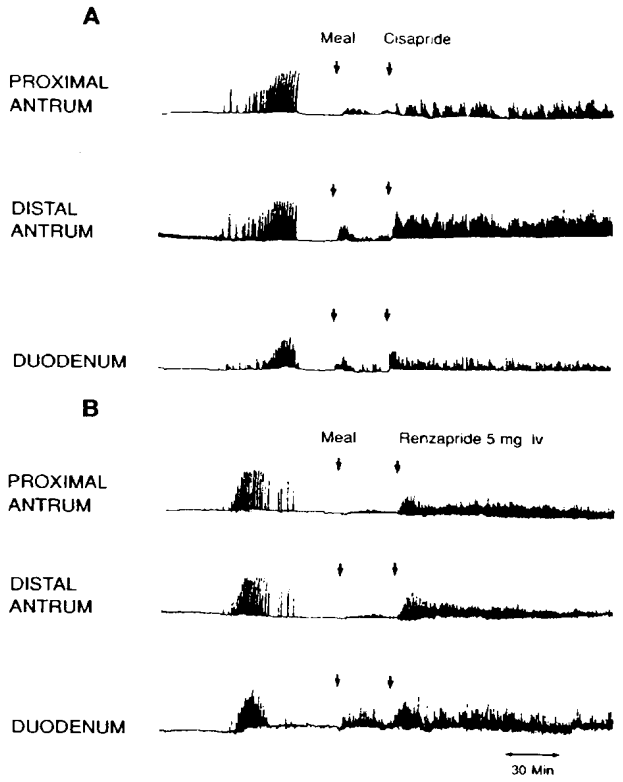

Fig. 4. Effect of i.v. cisapride (panel A) or renzapride (panel B) on the postprandial motility of the gastric antrum and duodenum of one dog. Cisapride or renzapride enhanced the contractile activity of the antrum and duodenum during the digestive state.

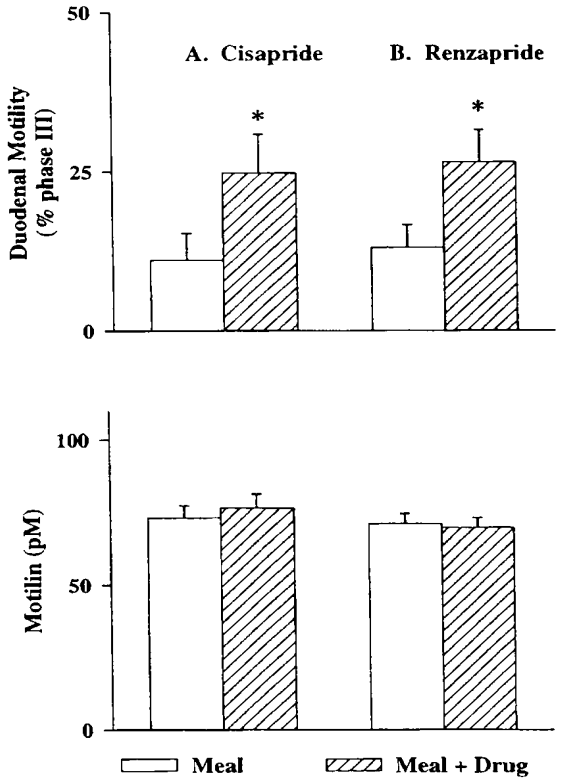

Fig. 5. Mean changes in duodenal motility and plasma motilin concentration in response to cisapride (panel A) or renzapride (panel B) during the postprandial state. Mean postprandial plasma motilin levels during the first 30 min after drug administrations were not different from that observed 30 min before drug, whereas significant augmentation of digestive motility occurred. *P < .01.

release of ACh at nerve endings in the myenteric plexus (Pfeuffer-Friederich and Kilbinger, 1984; Van Nueten *et al.*, 1984). In the guinea pig ileum strip, a transient increase, induced by cisapride, in the release of ACh was abolished in the presence of serotonin (Pfeuffer-Friederich and Kilbinger, 1984). The facilitating effect of serotonin on ACh release was reduced by cisapride also (Pfeuffer-Friederich and Kilbinger, 1984). Thus cisapride was claimed to be a weak agonist of both excitatory and inhibitory serotonin receptors (Pfeuffer-Friederich and Kilbinger, 1984) or a serotonin receptor blocker (Van Nueten *et al.*, 1984). Renzapride also increased electrically evoked cholinergically mediated contractions, probably by increasing ACh release (Sanger, 1987). This action of renzapride was prevented by a high concentration of serotonin, but not by hexamethonium, phentolamine, propranolol or methysergide (Sanger, 1987). It has also been suggested that these new benzamide compounds exert their motility-stimulating actions *via* an agonistic effect on serotonin-4 receptor (Craig and Clarke, 1990; Craig and Clarke, 1991; Ford and Clarke, 1993; Gullikson *et al.*, 1993; Meulemans and Schuurkes, 1992; Taniyama *et al.*, 1991) or a nonserotonergic mechanism (deRidder and Schuurkes, 1993). Because some of the enterochromaffin cells contain motilin as well as serotonin (Kishimoto *et al.*, 1981), the serotonin-4 receptor agonistic actions of the two benzamides may have a regulatory role on the release of motilin from the enterochromaffin cells.

It was recently discovered that the mechanism of GI prokinetic action of metoclopramide, another benzamide, is through the activation of serotonin-4 receptors (Ford and Clarke, 1993), not *via* dopamine blocking action. So far, three different investigators have examined the effect of metoclopramide on motilin release in the human (Achem-Karam *et al.*, 1985; Grandjouan *et al.*, 1989; Rees *et al.*, 1982). All three investigators agreed on its prokinetic action on the GI tract, but only Achem-Karam *et al.* (1985) reported that it stimulated motilin release. The reason for these conflicting results is not clear. Further investigation will be needed.

The stimulatory effect of renzapride on gastroduodenal motility suggests that, like cisapride (Kawagishi *et al.*, 1993; Krevsky *et al.*, 1989; McHugh *et al.*, 1992), it may have useful clinical application to improve motility disorders associated with gastroparesis and/or disturbed gastroduodenal coordination. Renzapride may join such well-established prokinetic drugs as cisapride and metoclopramide.

In conclusion, both cisapride and renzapride increased plasma motilin levels and gastroduodenal motility simultaneously in the interdigestive state, whereas in the postprandial state, although both increase gastroduodenal motility, neither one influenced the plasma concentration of motilin. Like cisapride, renzapride may exert similar stimulatory effects on gastroduodenal motility in humans. Thus it may become a useful prokinetic agent.

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Dual effects of cisapride on gastric emptying and antropyloroduodenal motility

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Fraser, R., M. Horowitz, A. Maddox, and J. Dent. Dual effects of cisapride on gastric emptying and antropyloroduodenal motility. *Am. J. Physiol.* 264 (*Gastrointest. Liver Physiol.* 27): G195-G201, 1993.—There is little information about the effects of cisapride on human antropyloroduodenal motility, despite its documented efficacy for increasing the rate of gastric emptying in patients with gastroparesis. Cisapride has been reported to have little effect on gastric emptying in normal subjects. Antral, pyloric, and duodenal pressures were recorded simultaneously with gastric emptying in 20 healthy volunteers. Thirty minutes after the solid component of the meal had started to empty from the stomach, each subject received either 10 mg cisapride iv (11 subjects) or intravenous saline (9 subjects). Intravenous saline had no effect on either motility or gastric emptying. In contrast, cisapride administration was associated with a dual effect on motility, with initial suppression of antral pressure waves ($P < 0.05$) followed by stimulation of associated antropyloroduodenal pressure waves ($P < 0.01$). Gastric emptying slowed in the first 30 min after cisapride ($P < 0.05$), and this was followed by more rapid gastric emptying ($P < 0.01$). The amount of the meal emptied in the 60 min after cisapride correlated with the number of associated antroduodenal pressure waves ($r = 0.75$, $P < 0.001$) but not with the number of antral waves ($r = 0.42$, NS). These results indicate that cisapride in a dose of 10 mg iv has dual effects on gastric emptying and gastric motility. **The stimulation of associated antral pressure waves is a plausible mechanism** for the efficacy of cisapride in the treatment of gastroparesis.

gastroparesis; pressure waves

GASTROPARESIS IS NOW RECOGNIZED to be a frequent cause of upper gastrointestinal symptoms such as anorexia, nausea, vomiting, and early satiety (12). In patients with diabetes mellitus, disordered gastric emptying may affect the control of blood glucose concentrations adversely, by causing mismatch between the timing of insulin administration and nutrient absorption from the small intestine (13).

Drug therapy has been the most effective approach to treatment of gastroparesis and in this respect the substituted benzamide cisapride appears to offer a major advance in therapy (12, 23). This drug accelerates gastric emptying in essentially all forms of gastroparesis (3, 4, 6, 9, 15, 16, 19, 32, 37), and this action appears to be sustained (4, 6, 23) unlike that of other drugs (14, 20, 28). Cisapride also has beneficial effects on disordered motor function in other areas of the gastrointestinal tract (3, 4, 10). During oral administration, cisapride, unlike metoclopramide, appears to be associated with few and trivial side effects (23).

There is relatively little information about the gastric motor correlates of the increased rate of gastric emptying caused by cisapride in patients with gastroparesis (22, 26, 27). In healthy humans, gastric emptying has been variably reported to be unchanged (8) or accelerated (3, 21) after cisapride, with the consensus that the drug has little effect on gastric emptying, particularly of solid meals, in healthy humans (23). We have now performed concurrent measurements of antropyloroduodenal pressures and gastric emptying in healthy volunteers before and after cisapride administration and demonstrated for the first time a dual effect of this drug on gastric emptying and antral motility.

METHODS

Subjects. Studies were performed in 20 healthy volunteers (11 men, 9 women; aged 18-27 yr, 50-81 kg), who had no history of gastrointestinal disease and were not taking any medication. The study was approved by the Human Ethics Committee of the Royal Adelaide Hospital. Written informed consent was obtained from each subject.

Protocol. On the morning after an overnight fast, a manometric assembly was passed transnasally, and its position across the pylorus was verified with dual point transmucosal potential difference (TMPD) measurements. After the catheter had been positioned correctly, all subjects ingested a radioisotopically labeled test meal. Approximately 30 min after the solid component of the meal had started to empty from the stomach, each subject received an intravenous injection of either 10 mg cisapride dissolved in 10 ml of 5% dextrose (11 subjects) or 10 ml of normal saline (9 subjects) over 10 min. Manometric and scintigraphic recordings were continued for 60 min after the intravenous injection and evaluated without knowledge of the treatment (saline or cisapride) that had been used in the study under analysis.

Manometric measurements. The manometric technique was similar to that described in other studies (10, 11, 17). Pressures were measured with a 10 lumen perfused manometric catheter, which incorporated a 4-cm sleeve sensor in parallel with an array of sideholes. Sideholes at each end of the sleeve recorded intraluminal pressure and TMPD simultaneously and were referred to as the antral and duodenal TMPD sideholes (10, 17). Pressures from the TMPD sideholes taken in conjunction with two sideholes along the sleeve allowed discrimination of localized pyloric contractions. Sideholes located 2, 4, and 6 cm proximal to the sleeve, and a sidehole 2 cm distal to the sleeve recorded antral and proximal duodenal pressure, respectively.

Manometric channels were perfused with degassed liquid at 0.3 ml/min with an adapted pneumohydraulic pump. The antral and duodenal TMPD channels were perfused with normal saline from separate reservoirs; all other channels were perfused with distilled water from a third reservoir. Pressures were recorded with pressure transducers (catalog no. 38/8000/1: Deseret Medical, Sandy, UT) interfaced to a 12-channel chart recorder (model 7D; Grass, Quincy, MA), which was run at a paper speed of 100 mm/min. TMPD was measured via the saline columns that perfused the antral and duodenal TMPD sideholes. TMPD measurements were recorded continuously on the chart recorder throughout the experiment. Records were only analyzed when the sleeve was correctly positioned across the pyloric TMPD gradient. Assembly position was taken as correct when antral TMPD was less than or equal to −20 mV, duodenal TMPD was greater than or equal to −15 mV, and the difference between the two was at least 15 mV (10, 17). Records were divided into

15-min periods, with *time 0* the start of the intravenous injection. Pressure waves were counted if their amplitude was ≥10 mmHg.

The number of pressure waves recorded in the antral TMPD sidehole was counted to provide a simple motility index (10, 11, 17). Waves recorded by the sleeve spanning the pylorus were classified as isolated pyloric pressure waves (IPPWs), when they occurred in the absence of a pressure wave of any magnitude in the antral or duodenal sideholes and were seen in no more than one sidehole along the sleeve (11). As in previous studies, basal pyloric pressure was referenced to distal antral pressure and was measured for the first 30 s of each minute of each study. The mean of these values was calculated for each 15-min interval (10, 17). Duodenal motility was evaluated by counting the number of pressure waves recorded by the distal duodenal sidehole and determining the median frequency of these pressure waves for particular time periods (10, 17).

Antral and duodenal pressure waves were judged to be associated in time if the onset of the pressure wave recorded in one sidehole occurred within 5 s of the onset of a pressure wave recorded in an adjacent sidehole (17). The luminal distance over which associated waves occurred was determined from the sidehole spacing of the manometric assembly (17) and the number of associated antral pressure waves ≥6 cm in length (long waves) was determined for each 15 min of the study.

Measurement of gastric emptying. Gastric emptying was measured with a previously described technique (5). Each test meal was ingested at ~1300 h. The study was performed in the sitting position with a scintillation camera behind the subject. The solid meal consisted of 100 g of cooked ground beef mixed with chicken liver labeled in vivo with ^{99m}Tc sulfur-colloid. The total caloric content of the solid meal was ~270 kcal (25 g protein, 21 g fat). The unlabeled liquid component of the meal was 150 ml of 10% dextrose. Corrections were made for patient movement, gamma ray attenuation, and radionuclide decay (5). Gastric emptying curves for the solid component of the meal, expressed as the percentage remaining within the stomach over time, were derived. Calculations were made of the duration of the lag phase (before any of the solid meal emptied from the stomach) and the amount of the solid meal that emptied from the stomach in the 30-min interval before the intravenous injection and the two 30-min intervals immediately after the injection.

Statistical analysis. Data within each group were analyzed using the two-tailed Wilcoxon matched pairs signed-rank test and between groups with a two-way analysis of variance for each 30-min period. Relationships between emptying and motility in the 60 min after the intravenous injections were evaluated using the Pearson correlation coefficient. A P value of <0.05 was considered significant in all analyses. All values are expressed as median and interquartile range.

RESULTS

Nasogastric intubation and ingestion of the test meal were well-tolerated by all subjects. Approximately 15 min after completion of the cisapride injection, two volunteers complained of lightheadedness and nausea. In both instances these symptoms resolved promptly when the subjects lay flat. Data from these two subjects were excluded from analysis. The remaining nine subjects who received cisapride did not report any adverse effects. No adverse effects were reported after intravenous saline.

Pressure waves. There was no significant difference between the two groups in the number of antral and associated antral waves ≥6 cm long in the 30-min interval before the saline or cisapride injection (Figs. 1 and 2).

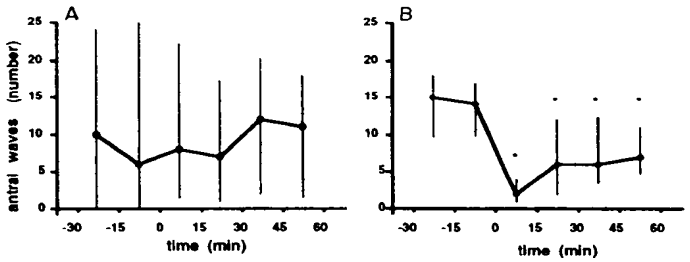

Fig. 1. Group data for total number of antral pressure waves (median values and interquartile ranges for 15-min time intervals) for intravenous saline-treated (*A*) and intravenous cisapride-treated (*B*) subjects. Intravenous saline had no effect. After intravenous cisapride there is a decrease in total number of antral pressure waves between 0 and 30 and 30 and 60 min, compared with pretreatment and intravenous saline ($*P < 0.05$).

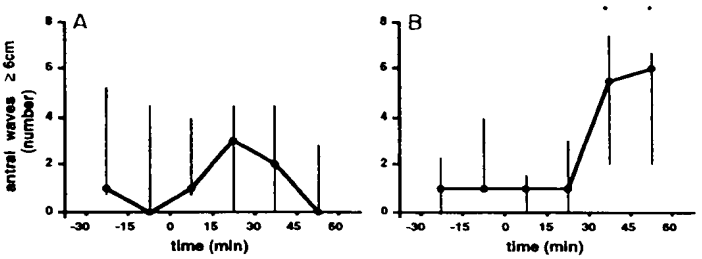

Fig. 2. Group data for number of associated antral pressure waves ≥6 cm long (median values and interquartile ranges for 15-min time intervals) for intravenous saline-treated (*A*) and intravenous cisapride-treated (*B*) subjects. Intravenous saline had no effect on number of waves ≥6 cm. After intravenous cisapride there is a decrease in number of antral pressure waves ≥6 cm between 0 and 30 min and an increase between 30 and 60 min, compared with −30–0 min and intravenous saline ($*P < 0.01$).

A representative example of a manometric recording around the time of the saline injection is shown in Fig. 3. Pressure patterns are typical for the postprandial period, with a number of pressure waves occurring in the distal antrum. Isolated pyloric and proximal duodenal pressure waves also occurred intermittently. In contrast, cisapride injection initially suppressed pressure waves in all manometric channels (Fig. 4). This inhibition was seen in all subjects and persisted for between 10 and 30 min. After this period of total pressure wave suppression, there was an increased number of associated antral pressure waves (Fig. 5).

The group data for the total number of antral pressure waves and the number of associated antral waves ≥6 cm in extent are shown in Figs. 1 and 2. Intravenous saline had no effect on either of these parameters. There was a reduction in the number of antral waves in both the first ($P < 0.01$) and the second 30-min interval ($P < 0.05$) after cisapride. The number of pressure waves ≥6 cm long also decreased in the 30-min period immediately after intravenous cisapride administration ($P < 0.05$) but was higher in the second 30 min after cisapride ($P < 0.05$) compared with both pretreatment values (−30–0 min) and the comparable time periods after intravenous saline.

In the first 15 min after cisapride, there was a decrease in IPPWs in eight of the nine subjects and a decrease in the number of duodenal pressure waves in seven of the

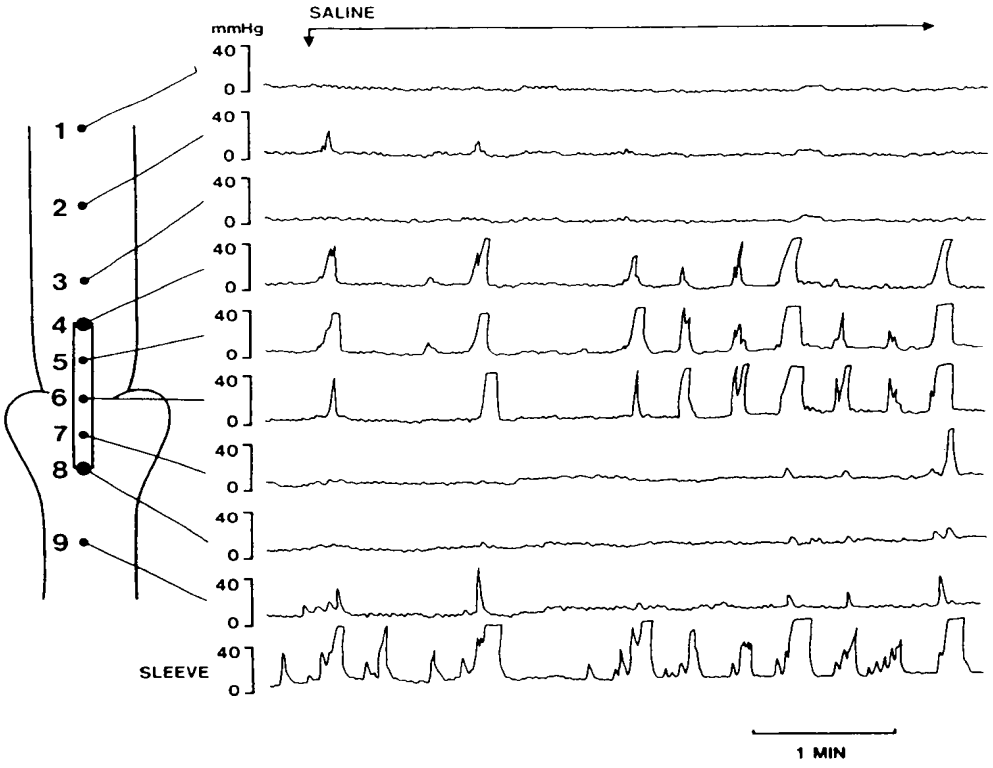

Fig. 3. Representative manometric tracing during emptying immediately after injection of intravenous saline. Schema on left shows approximate position of manometric channels. Predominant pattern consists of pressure waves in distal antrum with some associated pyloric and duodenal pressure waves.

nine subjects, but these changes did not achieve statistical significance ($P = 0.09$ and $P = 0.10$, respectively, Table 1). Cisapride had no significant effect on basal pyloric pressure (Table 1).

Gastric emptying. In the subjects who received saline, the median duration of the lag phase for the solid meal was 50 min (41-78 min). After the lag phase, the emptying curve approximated a linear pattern. There were no significant differences between the amount of the meal emptied in the 30 min before and either of the two 30-min periods after intravenous saline (Fig. 6), and 40% (37-48%) of the meal emptied in the 60 min after intravenous saline.

In the subjects who received cisapride, the median duration of the lag phase was 56 min (39-64 min), and the amount emptied in the 30-min interval before cisapride was 17% (13-24 min). Neither of these values differed from the respective ones in the intravenous saline-treated group (P = NS). Figure 6 shows the gastric emptying curve from a subject before and after intravenous cisapride. There is virtual cessation of gastric emptying for ~15 min after cisapride, followed by more rapid emptying until the end of the study. Figure 7 shows the group data for emptying. There was a decrease in the amount emptied in the first 30 min after cisapride ($P < 0.05$), followed by an increase in emptying in the subsequent 30 min ($P < 0.01$). The amount of the meal emptied in the 60 min after cisapride was 40% (34-59%), which was not significantly different from the intravenous saline-treated group.

Relationship between pressure waves and emptying. In the 60 min after intravenous saline, the amount of the meal emptied did not correlate significantly with the number of antral pressure waves ≥6 cm long ($r = 0.38$, P = NS) or the number of antral pressure waves ($r = 0.10$, P = NS). After intravenous cisapride there was a significant correlation between the amount of the meal emptied and the number of antral waves ≥6 cm in length ($r = 0.75$, $P < 0.001$; Fig. 8), but not with the number of antral pressure waves ($r = 0.42$, P = NS).

DISCUSSION

The major new findings in this study are that in healthy humans *1*) the acceleration of gastric emptying caused by cisapride is related to a pattern of antropyloroduodenal pressure waves, which resembles that recorded during fasting and *2*) intravenous cisapride in a dose of 10 mg has dual effects on antroduodenal motility and gastric emptying.

The acceleration in gastric emptying after cisapride occurred even though there was a reduction in the number of antral pressure waves. There was a close relationship between the number of associated antral, pyloric, and duodenal pressure waves and the rate of gastric emptying. Earlier studies in patients with gastroparesis have reported that cisapride administration is associated with an increase in the antral motility index (3). Such an index reflects both the frequency and amplitude of antral contractions but does not provide an indication as to the organization of antral contractions. This is a major limitation, because it is clear that antral contractions have markedly different results on movement of luminal content, ranging from powerful expulsion into the duodenum during fasting that is not selective for particle size to a totally retropulsive, triturative contractile pattern (25). Our results suggest that cisapride stimulates a specific

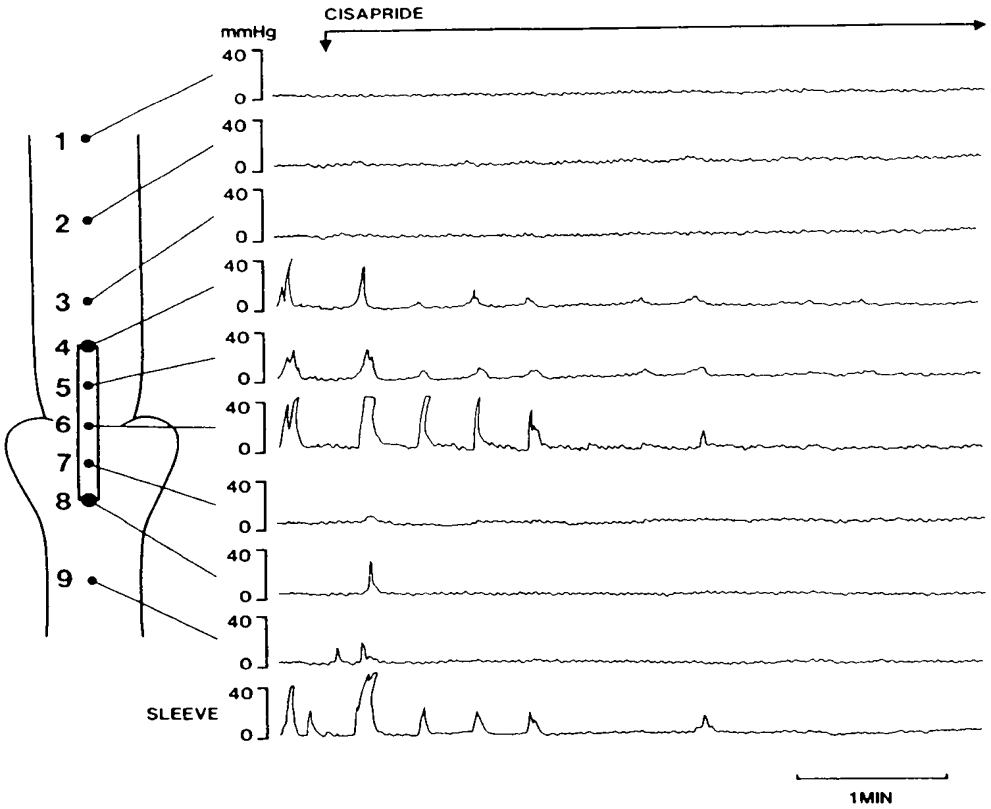

Fig. 4. Example of immediate effect of cisapride on antropyloroduodenal motor patterns. For details of schema on left see Fig. 3 legend. There is suppression of pressure waves in all manometric channels.

pattern of motility, in which contractions begin higher in the gastric antrum and extend across the pylorus in a manner similar to that seen during gastric phase III in the interdigestive state (17). Although an increased number of temporally associated antral pressure waves has been postulated as a mechanism for the beneficial effects of cisapride on postprandial gastric emptying (29, 31), this has not previously been demonstrated in humans. If similar effects occur after cisapride administration in patients with gastroparesis, this motor pattern is likely to contribute to the documented beneficial effects of cisapride (23).

Recent studies suggest that the pylorus is important in the regulation of gastric emptying (10, 36) and an increased number of isolated pyloric contractions has been reported to occur in some patients with gastroparesis (24). Cisapride has been reported to reduce the incidence of localized pyloric contractions in dogs (7). In our study, phasic and tonic pyloric contractions were relatively infrequent making evaluation of the effect of cisapride on pyloric motility difficult. There was, however, a nonsignificant decrease in the number of isolated pyloric pressure waves immediately after intravenous cisapride administration.

The initial inhibition of antral and duodenal motility and gastric emptying after intravenous cisapride was unexpected. The possibility that these observations were due to intravenous injection, rather than to cisapride as such seems unlikely in view of the fact that intravenous saline injection did not affect motility. Previous studies in healthy volunteers and patients with gastroparesis have suggested that cisapride stimulates antral and small intestinal contractions and increases the antral motility index (3, 26, 27). In addition to the limitations of an antral motility index, the design of these studies does not exclude transient suppression of antral motility by cisapride. For example, the study of Reboa et al. (26) was performed during fasting in which there are long periods of motor quiescence, and a reduction in motor activity may therefore not be noted. Camilleri et al. (3) reported an overall increase in the antral motility index after cisapride in fed healthy subjects, but there may have been a period of suppression that was masked by the subsequent stimulation. In patients with gastroparesis, it is likely to be difficult to demonstrate inhibition of antral contractions, as these are often reduced (3, 27). Therefore the discrepancy between our results and previous studies is likely to be apparent rather than real. It is of note that Stacher et al. (32) reported a small but statistically significant decrease in the frequency of antral contractions (evaluated scintigraphically) in healthy humans after 8 mg cisapride iv. In this study, however, recordings commenced 30 min after cisapride administration. The relatively small effect of cisapride on overall gastric emptying in normal subjects (8, 21) has been attributed to the difficulty in overriding the feedback mechanisms regulating gastric emptying (23). Most of these studies have only reported the 50% emptying time, and gastric emptying over smaller time intervals has not been examined. Our results suggest that this lack of effect on emptying may be due to dual effects on gastroduodenal motility and that the overall result is to produce only minimal alteration of gastric emptying times in healthy humans.

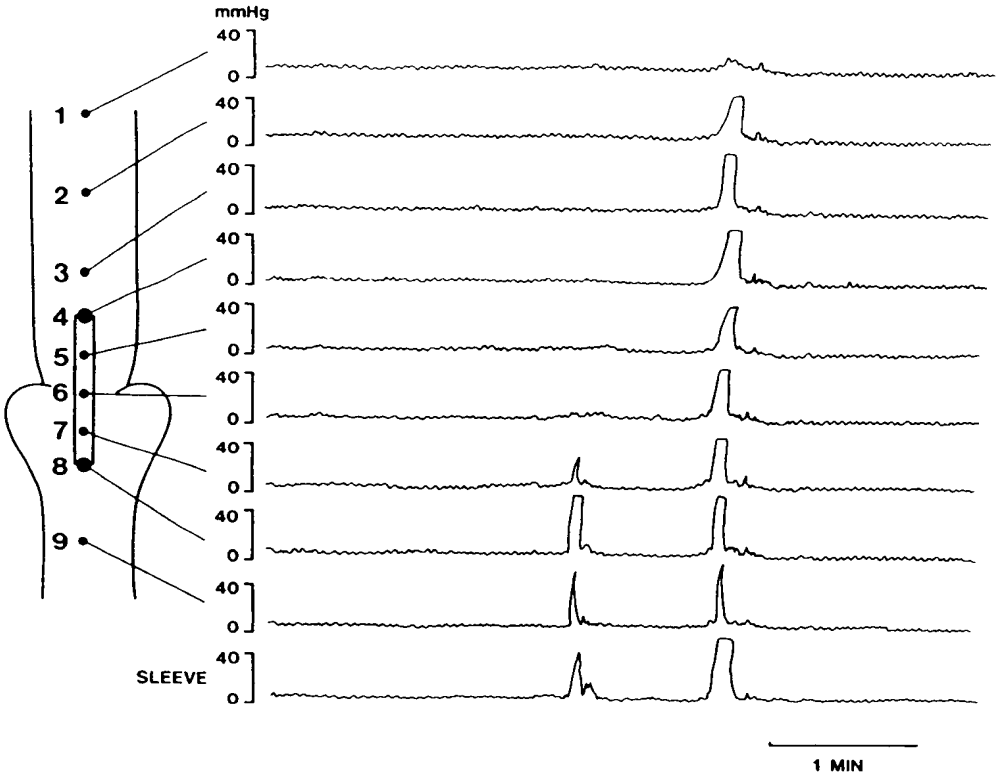

Fig. 5. Example of manometric pattern 30 min after cisapride administration. For details of schema on left see Fig. 3 legend. There are few antral pressure waves and an associated antral pressure wave ≥6 cm is evident.

The present study does not give insights into the mechanisms underlying the inhibitory effects of cisapride. Cisapride is believed to stimulate gastrointestinal smooth muscle indirectly, via the release of acetylcholine from myenteric nerves (23). Cisapride has been shown to have serotonin $(5\text{-HT})_3$ antagonist, 5-HT_4 agonist, and non-5-HT effects (30, 34). The 5-HT_3 antagonist properties do not appear imperative for its gastric prokinetic actions (30). A recent study suggests that cisapride enhanced contractions in canine longitudinal muscle strips by a mechanism that does not involve serotonergic mechanisms (30). The effects of cisapride on motility are dose related (34). In vitro studies of guinea pig ileum have demonstrated 5-HT_1 antagonism at low concentrations, 5-HT_3 antagonism and 5-HT_4 agonism at medium concentration, and 5-HT_4 agonism at high drug concentrations (34). It is unlikely that the inhibitory effects we recorded were due to unusually high levels of acetylcholine at the neuromuscular junction, because previous studies in animals have not shown inhibition of gastric motility during direct stimulation with acetylcholine (1). After intravenous administration, cisapride has a triphasic distribution profile, with the first phase lasting 20–30 min. Our findings could possibly be due to the relatively high blood concentrations of cisapride immediately after injection. In studies in dogs, Schuurkes and van Nueten (31) reported that oral cisapride, in a dose of 1.25 mg/kg, caused a 20% reduction in antral contraction frequency. In addition, Tonini et al. (35) showed that high concentrations of cisapride reduced the contraction amplitude in an in vivo preparation of guinea pig ileal smooth muscle. These effects may reflect an action of cisapride on inhibitory nerves within the myenteric plexus or on the smooth muscle itself. The serum levels observed immediately after an intravenous dose of 10 mg cisapride are considerably higher than those obtained with conventional oral dosage (23). Therefore the relevance of our observations to clinical practice is uncertain.

Table 1. *Effect of saline and cisapride on pyloric and duodenal motility*

	Time, min		
	−30-0	0-30	30-60
Saline			
IPPWs, no.	4 (2-10)	4 (3-7)	7 (3-10)
Basal pyloric pressure, mmHg	0.8 (0.3-1.5)	0.4 (0-0.7)	0.9 (0.3-1.1)
Duodenal pressure waves, no.	56 (33-78)	57 (43-82)	55 (33-91)
Cisapride			
IPPWs, no.	11 (10-22)	10 (5-24)	15 (6-29)
Basal pyloric pressure, mmHg	0.3 (0.2-1.0)	0.5 (0.3-1.3)	−0.3 (−0.5-0.8)
Duodenal pressure waves, no.	36 (25-45)	24 (18-31)	33 (26-42)

Effect of intravenous saline and cisapride injections on phasic and tonic pyloric pressure waves and duodenal pressure waves. Intravenous injections were given at *time 0*. IPPWs, isolated pyloric pressure waves. Data are median values; nos. in parentheses are interquartile ranges. There are no significant differences.

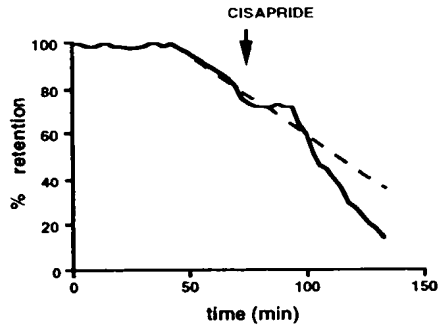

Fig. 6. Example of gastric emptying curve from a subject treated with intravenous cisapride. Note slowing (and virtual cessation) of gastric emptying for ~15 min, followed by more rapid gastric emptying until end of study. The "theoretical" normal linear emptying is illustrated by the dashed line.

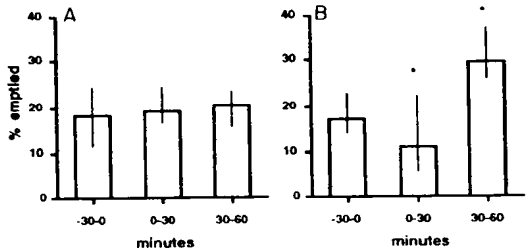

Fig. 7. Group data for solid gastric emptying for (median values and interquartile ranges for 30-min time intervals) intravenous saline-treated (*A*) and intravenous cisapride-treated (*B*) subjects. Intravenous saline had no effect on solid emptying. After intravenous cisapride administration, there was a decrease in amount emptied between 0 and 30 min compared with −30-0 min (*$P < 0.05$) and an increase in emptying between 30 and 60 min compared with −30-0 min (*$P < 0.01$).

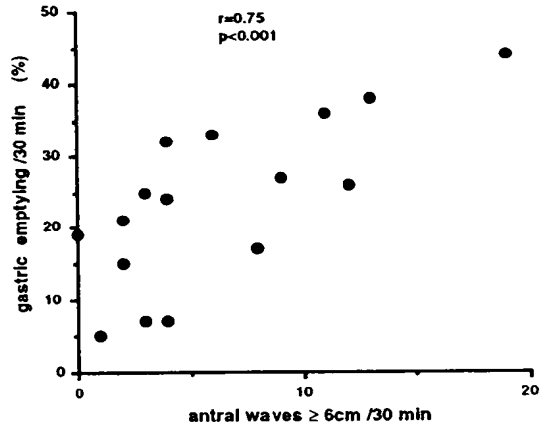

Fig. 8. Relationship between gastric emptying and number of associated antropyloroduodenal pressure waves ≥6 cm long in the first 60 min (two 30-min intervals) after intravenous cisapride ($r = 0.75$, $P < 0.001$).

The etiology of the lightheadedness and nausea reported by two of our volunteers is unclear. Transient faintness and dizziness have been reported after parenteral administration of cisapride (18, personal communication from Dr. M. Verlinden). It seems unlikely that these feelings represent a vasovagal response to intravenous injection per se, because none of the saline-treated patients developed similar symptoms. Since the symptoms resolved quickly when the subjects lay flat, they are most likely to have a cardiovascular cause and may have become apparent because our subjects were studied after a meal and in the erect posture. Bateman (2) reported that intravenous cisapride produced transient falls in blood pressure and an increase in heart rate of ~10 beats/min, possibly as a result of vasodilation. Further circumstantial support for this concept of vasodilatation comes from a study by Horowitz et al. (15), in which a group of patients with systemic sclerosis reported improvement of Raynaud's phenomenon while taking cisapride. These cardiovascular effects may be due to action of cisapride as a 5-HT antagonist (18, 34). There have been no reports of similar adverse effects with oral cisapride in doses ≤40 mg/day (18, 23, 33), and it is therefore likely that they are due to the high serum drug levels initially produced by intravenous administration.

In conclusion, we have shown that cisapride when administered intravenously in a dose of 10 mg has dual effects on both gastroduodenal motility and gastric emptying. The stimulation of associated antropyloroduodenal waves ≥6 cm in extent recorded subsequent to the initial inhibition may be responsible for the beneficial effects of cisapride in patients with gastroparesis.

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The influence of cisapride on gastric tone and the perception of gastric distension

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SUMMARY

Background: Delayed gastric emptying, impaired gastric accommodation to a meal and hypersensitivity to gastric distension have been implied in the pathophysiology of functional dyspepsia. Dyspeptic patients are often treated with the prokinetic drug cisapride.

Aim: To assess the effects of cisapride on perception of gastric distension and gastric accommodation to a meal.

Methods: Eighteen healthy volunteers underwent a gastric barostat study on two occasions, after pre-treatment with placebo or cisapride 10 mg q.d.s. Graded isobaric and isovolumetric distensions were performed until the subjects reported discomfort. Volume and pressure changes were recorded and perception was scored by a questionnaire. In 10 volunteers, the amplitude of the gastric accommodation to a mixed liquid meal was also measured.

Results: Pre-treatment with cisapride significantly lowered thresholds for perception and for discomfort, both during isobaric (4.3 ± 0.7 vs. 3.2 ± 0.7 and 12.2 ± 1.2 vs. 9.2 ± 0.9 mmHg above minimal distending pressure (MDP), respectively, $P < 0.05$) and isovolumetric (256 ± 46 vs. 200 ± 35 and 644 ± 36 vs. 511 ± 40 mL, respectively, $P < 0.05$) distensions. Cisapride significantly enhanced the size of the meal-induced fundus relaxation (143 ± 37 vs. 270 ± 50 mL, $P < 0.05$).

Conclusions: Cisapride enhances both the perception of gastric distension and the gastric accommodation to a meal. These data suggest that cisapride may provide benefit to patients with impaired postprandial relaxation of the fundus.

INTRODUCTION

Functional dyspepsia is a clinical syndrome defined by chronic or recurrent upper abdominal symptoms without identifiable cause by conventional diagnostic means (endoscopical, radiological, histological).[1] The symptom complex is related to feeding and includes epigastric pain, bloating, early satiety, fullness, anorexia, belching, nausea and vomiting.[2]

The pathophysiology of functional dyspepsia is not fully established, but a number of putative mechanisms have been suggested. Pathophysiological disturbances that have been reported in patients with functional dyspepsia include delayed gastric emptying with abnormal postprandial antral motility, hypersensitivity to gastric distension and impaired postprandial relaxation of the gastric fundus.[2–9] Each of these disturbances have been reported to be present only in subgroups of functional dyspepsia patients.

Because of its ability to enhance gastric emptying, dyspeptic patients are often treated with the prokinetic drug cisapride.[10, 11] Notwithstanding the occurrence of delayed gastric emptying and antral hypomotility in dyspeptic patients, this cannot completely account for the symptoms because a large proportion of patients have perfectly normal gastric emptying.[3, 12] The effects

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of cisapride on the perception of gastric distension and on postprandial fundus relaxation, two major pathophysiological mechanisms in dyspepsia besides delayed gastric emptying, are unknown.

The aim of the present study was to study the effect of cisapride on the sensitivity to gastric distension and on postprandial proximal stomach relaxation in a group of healthy volunteers.

MATERIALS AND METHODS

Study subjects and study design

Eighteen healthy volunteers (12 males and six females, age 20–29 years) participated in the study. They underwent a gastric barostat study on two separate occasions, after pre-treatment for 5 days with placebo or cisapride 10 mg q.d.s. None of the subjects had symptoms or a history of gastrointestinal disease or drug allergies, nor were they taking any medication. Informed consent was obtained from each participant. The order of placebo and cisapride treatment was randomized by drawing cards from a box of cards determining the sequence. The medication was administered by a study nurse who was otherwise not involved in the study. Half of the subjects received placebo first; the other half received cisapride first. The protocol had been previously approved by the Ethics Committee of the University Hospital.

Recording technique

Following an overnight fast of at least 12 h, a double lumen polyvinyl tube (Salem sump tube 14 Ch., Sherwood Medical, Petit Rechain, Belgium) with an adherent plastic bag (1200 mL capacity, 17 cm maximal diameter) which was finely folded, was introduced through the mouth and secured to the subject's chin with adhesive tape. The position of the bag in the gastric fundus was checked fluoroscopically.

The polyvinyl tube was then connected to a computer-driven programmable volume-displacement barostat device (Synectics Visceral Stimulator, Stockholm, Sweden). The barostat device can deliver volume ramps or pressure steps at different rates, while simultaneously monitoring pressure and volume at a sampling rate of 8/s. Pressure is monitored within the inflation device. To unfold the intragastric bag, it was inflated with a fixed volume of 500 mL of air for 2 min with the study subject in a recumbent position, and again deflated completely. After a 10 min equilibration period, the subjects were positioned in a comfortable sitting position with the knees slightly bent (80°) in a bed, specifically designed for that purpose.

Barostat study protocol

After a 30 min accommodation period, intrabag pressure was increased by 1 mmHg every minute to determine minimal intragastric distending pressure (MDP) as the lowest pressure level that provided an intrabag volume of 30 mL or more.[13] This pressure level equilibrates the intra-abdominal pressure. Subsequently, graded isobaric and isovolumetric distensions were applied in random order, with a 30 min accommodation period between the two series of distensions.

Sequential isobaric distensions were performed in stepwise increments of 2 mmHg, starting from MDP and each lasting for 2 min, while the corresponding intragastric volume was recorded. Subjects were instructed to score their perception of upper abdominal sensations induced by each distending stimulus at the end of every distending step, using a graphic rating scale that combined verbal descriptors on a scale graded from 0 to 6.[13] The end-point of each sequence of distensions was established at an intrabag volume of 1000 mL, or when the subjects reported discomfort or pain (score 5 or 6). Sequential isovolumetric distensions were performed in stepwise increments of 100 mL, each lasting for 2 min, while the corresponding pressure was recorded. The same perception score and distension end-points were applied.

In 10 volunteers, after another 30 min accommodation period, the pressure level was set at MDP + 2 mmHg. After 30 min, a mixed liquid meal (200 mL, 300 kcal, 13% proteins, 48% carbohydrates, 39% lipids; Nutridrink, Nutricia, Belgium) was administered. Measurement continued until the end of the meal-induced gastric relaxation.

Data analysis

Analysis of the barostat recordings was performed blindly on coded tracings. For each 2 min distending period, the dependent variable was calculated by averaging the recording. The thresholds for perception and discomfort were computed after the experiments, by analysing the perception score corresponding to each

distension step. Perception threshold was defined as the first level of pressure (during isobaric distensions) or the lowest volume (during isovolumetric distensions) that had evoked a perception score of 1 or more. Discomfort threshold was defined as the first level of pressure (during isobaric distensions) or the lowest volume (during isovolumetric distensions) that had provoked a perception score of 5 or more. Gastric compliance was calculated as the slope of the pressure–volume curve obtained by stepwise isobaric distensions.

To evaluate gastric tone before and after administration of the meal, the mean intra-balloon volume was calculated over consecutive 5 min intervals. The meal-induced gastric relaxation was quantified by calculating the difference between the average intragastric volume during the 30 min before and the first 60 min after the administration of the meal.[14] The maximum postprandial volume increase and the time needed to reach the maximum postprandial volume were calculated. In addition, the duration of the meal-induced relaxation (defined as the time needed before the intragastric volume is again at or below the mean preprandial volume) was also determined.

All numbers are given as mean ± S.E.M. MDP, gastric compliance and thresholds to gastric distension during cisapride and placebo were compared using the paired Student's *t*-test. Pressure-volume curves and distension-perception score curves after cisapride or placebo were compared by two-way ANOVA. The number of subjects that reported perception or discomfort at a given intragastric volume or pressure were compared before and after drug administration using a logistic regression procedure with stratification, implying exact conditional inference. The postprandial gastric relaxation curves were compared by two-way ANOVA. The meal-induced gastric relaxation, the maximum postprandial volume increase, the time needed to reach the maximum postprandial volume and the duration of the meal-induced relaxation were compared using the paired Student's *t*-test. Differences were considered to be significant at the 5% level.

RESULTS

Effect of cisapride on isovolumetric gastric distensions

Both after placebo and after cisapride, distensions of the stomach with progressively larger volumes produced progressively larger intragastric pressures (Figure 1). At the same distending volumes, intragastric pressures were significantly higher after pre-treatment with cisapride (ANOVA, $P = 0.01$). In addition, after cisapride, significantly higher perception scores were obtained for the same distending volumes (ANOVA, $P < 0.0005$) (Figure 2).

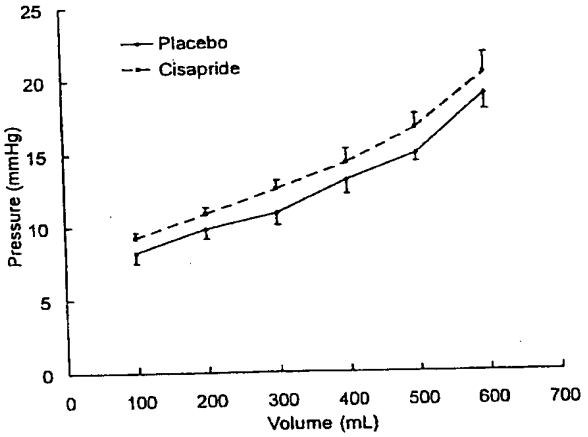

Figure 1. Pressure–volume relationship obtained by gradually increasing isovolumetric gastric distensions after treatment with placebo or cisapride ($n = 18$). Cisapride causes a shift of the volume–pressure curve towards significantly higher pressures ($P = 0.01$, two-way ANOVA).

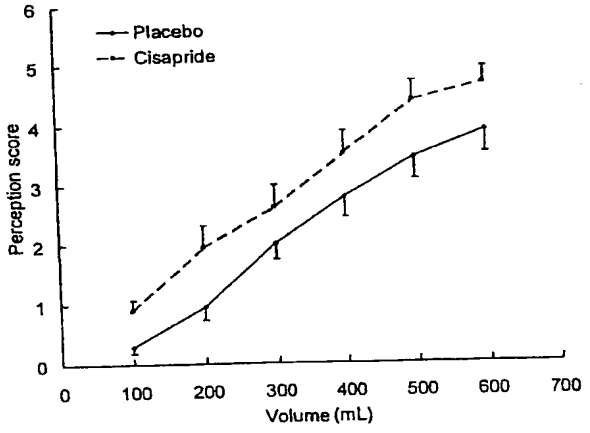

Figure 2. Corresponding mean perception scores for gradually increasing isovolumetric distensions after treatment with placebo or cisapride ($n = 18$). Cisapride significantly increases the average perception score at the same distending volumes ($P < 0.0005$, two-way ANOVA).

Pre-treatment with cisapride significantly decreased the perception thresholds (256 ± 46 vs. 200 ± 35 mL, $P < 0.05$) and discomfort thresholds (644 ± 36 vs. 511 ± 40 mL, $P < 0.001$) during isovolumetric distensions. The corresponding intragastric pressure at the threshold for perception (11.5 ± 1.5 vs. 11.2 ± 0.9 mmHg, N.S.) was not influenced, but the pressure at the threshold for discomfort (21.4 ± 1.4 vs. 17.8 ± 1.3 mmHg, $P < 0.01$) was significantly lowered by cisapride. Logistic regression analysis of volume–perception and volume–discomfort curves revealed a shift of the thresholds towards lower volumes after cisapride ($P < 0.05$).

Effect of cisapride on isobaric gastric distensions

Cisapride had no significant effect on MDP (7.4 ± 0.5 vs. 8 ± 0.5 mmHg, N.S.). Both after placebo and after cisapride, distensions of the stomach with progressively higher set pressures produced progressively larger intragastric volumes. Gastric compliance did not differ between placebo and cisapride (49.1 ± 6.7 vs. 52.5 ± 6.9 mL/mmHg). At the same distending pressures, intragastric volumes were significantly lower after cisapride (ANOVA, $P = 0.005$). In addition, after cisapride, significantly higher perception scores were obtained for the same distending pressures (Figure 3) (ANOVA, $P < 0.001$).

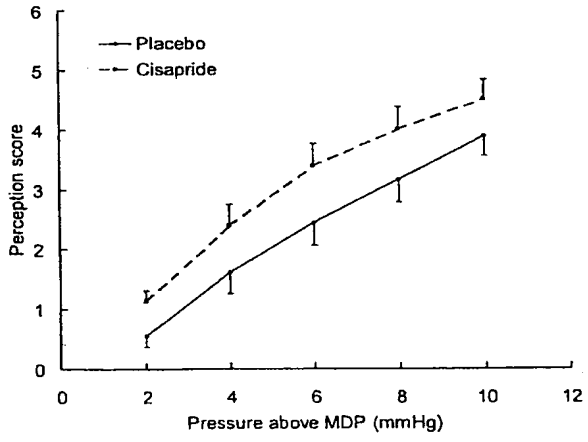

Figure 3. Corresponding mean perception scores for gradually increasing isobaric distensions after treatment with placebo or cisapride ($n = 18$). Cisapride significantly increases the average perception score at the same distending pressures ($P < 0.001$, two-way ANOVA).

Pre-treatment with cisapride significantly decreased the pressures needed to induce first perception (4.3 ± 0.7 vs. 3.2 ± 0.7 mmHg above MDP, $P < 0.05$) or discomfort (12.2 ± 1.2 vs. 9.2 ± 0.9 mmHg above MDP, $P < 0.005$) during isobaric distensions. The corresponding volumes at the threshold for perception (318 ± 39 vs. 227 ± 27 mL, $P < 0.05$) and at the threshold for discomfort (607 ± 42 vs. 517 ± 44 mL, $P < 0.05$) were significantly lower after cisapride treatment. Logistic regression analysis of pressure–perception and pressure–discomfort curves revealed that the thresholds were shifted towards lower distending pressures after cisapride ($P < 0.005$).

Influence of cisapride on the gastric accommodation to a meal

Before the meal, intragastric volumes after placebo or cisapride were similar (151 ± 20 vs. 162 ± 12 mL, N.S.) (Figure 4). After cisapride pre-treatment, significantly higher intragastric volumes were recorded postprandially (ANOVA, $P < 0.0001$). Cisapride significantly enhanced the amplitude of the meal-induced

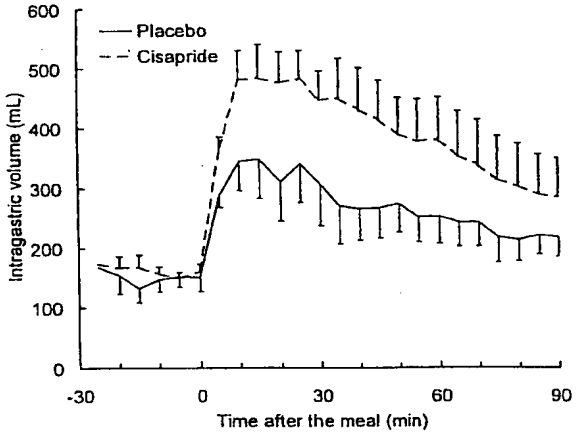

Figure 4. Influence of pre-treatment with cisapride on the meal-induced relaxation of the gastric fundus in 10 healthy subjects. During the 30 min preceding the meal, mean intragastric volumes in both groups were similar. After the meal, cisapride causes a significant shift towards larger intragastric volumes ($P < 0.0001$, two-way ANOVA). The meal-induced postprandial fundus relaxation, expressed as the difference between the average intragastric volume during the 30 min before and the first 60 min after the administration of the meal, was significantly enhanced by cisapride ($P < 0.05$).

fundus relaxation (mean 1 h postprandial volume increase 143 ± 37 vs. 270 ± 50 mL, $P < 0.05$) (Figure 4). The maximum volume increase after the meal (252 ± 46 mL after placebo and 386 ± 39 mL, N.S.), the time of the maximum postprandial relaxation (27 ± 6 and 38 ± 6 min after the meal, N.S.) and the duration of the meal-induced gastric relaxation (110 ± 9 and 111 ± 9 min, N.S.) did not differ significantly between placebo and cisapride.

DISCUSSION

Cisapride is frequently used in the pharmacological treatment of functional dyspepsia.[10, 11] The rationale for its use is its ability to enhance gastric emptying. However, in large studies, the percentage of dyspeptic patients with delayed gastric emptying ranges from 30 to 59%.[3, 5, 12] Therefore, pathophysiological mechanisms other than delayed gastric emptying are at least as important in causing dyspeptic symptoms. The other main pathophysiological disturbances that have been reported in patients with functional dyspepsia are hypersensitivity to gastric distension and impaired postprandial relaxation of the proximal stomach.[6–9, 14]

Because many dyspeptic symptoms are related to food ingestion, it has been hypothesized that functional dyspepsia may be caused by abnormal perception of gastric distension. In dyspeptic patients as a group, both the threshold for first perception and for pain during gastric distensions are significantly lower compared to normal controls.[6, 7] These data suggest that an altered gastric perception may be a mechanism of symptom production in functional dyspepsia. Hypersensitivity to gastric distension can be found in about 50% of the patients with functional dyspepsia.[7] Accommodation of the stomach to a meal consists of a relaxation of the gastric fundus and corpus, providing the meal with a reservoir and enabling a volume increase without a rise in intragastric pressure. Recent ultrasonographic and scintigraphic studies have demonstrated an abnormal distribution of food within the stomach of patients with functional dyspepsia, suggestive of an impaired gastric accommodation as an underlying mechanism.[8, 9, 14] Impaired postprandial relaxation of the proximal stomach is present in 40% of patients with functional dyspepsia. It is associated with symptoms of early satiety and weight loss.[14]

In the present study, we used a gastric barostat to examine the influence of cisapride on gastric sensitivity to distension and on the gastric accommodation to a meal. Cisapride enhanced the perception of both isobaric and isovolumetric gastric distensions. This occurred in the presence of a shift in volume–pressure relationships towards higher pressures for the same distending volume. These data suggest that cisapride is enhancing the fasting tone of the proximal stomach, which is probably contributing to the enhanced perception of gastric distension. An additional effect of cisapride on perceptive pathways cannot be ruled out. Obviously, enhanced perception of gastric distension does not seem beneficial to dyspeptic patients in whom hypersensitivity to gastric distension contributes to their symptoms. Therefore, studies on the relationship between visceral hypersensitivity and the clinical response to cisapride in patients with functional dyspepsia seem warranted.

In addition, we observed that cisapride enhances the meal-induced relaxation of the proximal stomach. Several mechanisms may contribute to this enhancement of gastric accommodation. Ingestion of nutrients causes a relaxation of the proximal stomach via a vagal reflex pathway, and it requires activation of intrinsic nitrergic neurones in the stomach.[15–17] Recent preliminary studies in the guinea pig have demonstrated that cisapride activates nitrergic pathways in the stomach.[18] A similar mechanism in man might explain the increased gastric accommodation to a meal after cisapride. An alternative explanation might be enhanced contractility of the gastric antrum induced by cisapride, thus causing a shift in the distribution of the meal towards the proximal stomach. An ultrasound study which demonstrated that cisapride reduces the postprandial antral area is in keeping with the latter hypothesis.[19] Intraduodenal instillation of nutrients, especially lipids, induces a vagally mediated relaxation of the proximal stomach.[15] Because of its gastroprokinetic properties, cisapride may enhance the gastric emptying of nutrients into the duodenum, thus enhancing reflex relaxation of the proximal stomach. Finally, the enhanced fasting tone of the proximal stomach during cisapride treatment may contribute to a larger rebound relaxation postprandially.

The effect of cisapride on the gastric accommodation to a meal may be relevant for its therapeutic effect in functional dyspepsia. Recently, we demonstrated that impaired postprandial relaxation of the proximal stomach is present in a high proportion of patients with functional dyspepsia, and that it is associated with

symptoms of early satiety and weight loss.[14] Enhancement of the gastric accommodation to a meal by cisapride is likely to be beneficial in these patients. Clinical studies have indeed confirmed that cisapride significantly improves early satiety in functional dyspepsia.[20]

In summary, we observed that cisapride lowers the thresholds for discomfort during gastric distension, and enhances the gastric accommodation to a meal in healthy subjects. These data suggest that cisapride may not be the preferred treatment for dyspeptic patients with hypersensitivity to gastric distension. However, cisapride may provide benefit in patients with impaired postprandial relaxation of the fundus.

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INFLUENCE OF ANTRAL CONTRACTION WAVES ON INTRAGASTRIC PRESSURE, FLUID MOTIONS AND MIXING.

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Recent high resolution concurrent manometry/MRI studies (Amer. J. Phisiol., to appear) have shown that active wall tone maintains constant background pressure and that slowed gastric emptying is confined primarily to periods of quiescence, suggesting that the primary function(s) of antral contraction wave (CW) activity may be other than gastric emptying. Detailed evaluation is difficult, however, in vivo. AIMS: To analyze the role of antral CW activity on intragastric fluid motions, pressure and mixing using computer simulations based on the laws of physics. METHODS: Two-dimensional computer simulations of a modeled stomach were carried out using the "lattice-Boltzmann" numerical method with specified time changes in stomach geometry. Single and multiple CWs were assumed to be born in the corpus and to increase in amplitude into the antrum. Fundic volume was made to decrease to match the computed rate of efflux. Gastric pressures and fluid motions were computed relative to a fixed duodenal pressure and fixed pyloric diameter. RESULTS: (1) calculated gastric pressure has space-time structure similar to manometrically measured pressure; (2) highest intragastric pressures are generated at the tips of the CWs; (3) contraction waves induce recirculation motions on either side of the CW that enhance mixing; (4) these recirculation motions are enhanced by multiple CWs; (5) a "zone of mixing" is created by the CWs that is confined to the antral CW region and into which drugs must be released to mix; (6) the zone of mixing and mixing levels are strongly affected by pyloric opening/closure history. CONCLUSIONS: Although antral peristaltic pressure waves can, in principle, contribute to gastric emptying, the contractions waves may play a more important physiological role in mixing gastric content. Drug mixing is strongly affected by the location of the capsule upon release, characteristics of antral wave activity, and coordination between antral contraction wave and pyloric opening history. Improvement in drug delivery may be possible by exploiting the sensitivities between mixing and gastropyloric mechanics. *Supported* by Janssen Research Found. USA, Swiss Nat. Science Found., Janssen-Cilag Switz.

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THE EFFECT OF ITOPRIDE ON PROXIMAL GASTRIC TONE AND VISCERAL PERCEPTION.

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Itopride is a newly developed prokinetic agent and has antidopaminergic and anti-acetylcholine esterase activities. Our aim was to evaluate the effect of itopride on proximal gastric tone and visceral perception. Methods: 15 healthy subjects participated in two experiments, 7 days apart in a randomized double blinded cross-over design with 3 days pretreatment of placebo or itopride. After fasting overnight, itopride was given prior to barostat study. The compliance curves were fit with a power-exponential model;$Vol = V_{max}*\exp[-(k*RelP)^{\beta}]$. The estimated pressures at $10\%(P_{0.1max})$ and $50\%(P_{0.5max})$ of estimated maximal volume(V_{max}) of the polyethylene bag were calculated from k and β. Minimal distending pressure(MDP) was defined as the pressure level that resulted in a corresponding volume of >30 ml. Sensory function was assessed by scoring the perception for nausea, fullness, and abdominal discomfort/pain during random-order distensions of 4, 8, and 12 mmHg above MDP. A 10 cm visual analog scale was used for each symptom and an aggregate perception score was calculated. Effects of distensions were studied three times. Results: Compliance ($P_{0.1max}$ and $P_{0.5max}$) was not different after pretreatment of itopride or placebo. Itopride had no effect on visceral perception at MDP + 4 mmHg (92.5 ± 45.3 vs. 79.1 ± 30.2), 8 mmHg (117.7 ± 41.1 vs. 118.9 ± 41.5) and at MDP + 12 mmHg(159.8 ± 43.9 vs. 149.9 ± 53.5). MDP and fasting tone were not different between the two groups. After itopride pretreatment, significantly higher intragastric volume was recorded during 60 min postprandial period(figure). Conclusion: Itopride enhances gastric accommodation to meals. This observation suggests that itopride may provide benefit to patients with impaired postprandial relaxation of the proximal stomach.

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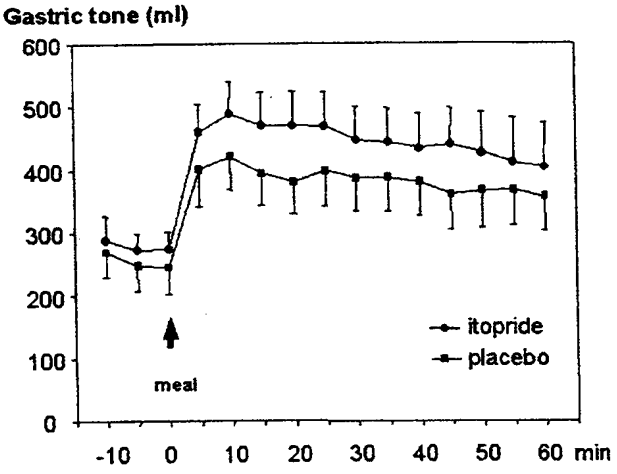

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PROLONGED INTRAGASTRIC DISTENTION IN HUMANS INDUCES PHASIC GASTRIC CONTRACTIONS DURING FASTING AND AFTER A MEAL.

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Introduction: Animal studies have shown that intragastric balloon distention induces phasic gastric contractions and lengthens phase II of the intestinal interdigestive motor cycle. In an ongoing study evaluating the effects of prolonged gastric distention on LES function by an intragastric balloon , we observed an increase in gastric contractile acivity. In the present study we characterized these contractions and evaluated their contribution to gastroesophageal reflux. Materials & Methods: Esophageal, LES, intragastric pressure and esophageal pH were studied in 18 obese females (21-56 yr) who received an intragastric balloon to reduce weight. The subjects had a body mass index of 42(31-50)$kg.m^{-2}$ and studies were performed before, immediately, 10 and 20 weeks after balloon placement. Results: Before balloon placement, phasic gastric contractile activity accompanied by an increase in LES pressure was observed in all subjects during fasting, but not after ingestion of a meal. None of the gastric contractions was accompanied by a reflux episode. Gastric contractions were not observed immediately after balloon placement. At 10 and 20 weeks of balloon placement 40% and 30% of the subjects reported to feel the balloon moving. On manometry, the time period with gastric contractile activity was significantly increased compared to before (36 (11-62)min vs 21(8-35)min) and 45% of the subjects had even phasic contractile activity for more than 1 hour. Interestingly, 60% (10wks) and 30% (20wks) of the subjects had also contractile activity after ingestion of a meal. In contrast to before balloon placement, 39% (10wks) and 40% (20wks) of the patients had one or more periods of gastro-esophageal reflux associated with a gastric contraction in the fasting and 33% (10 and 20 wks)in the postprandial period. 49% of these contractions was associated with a swallow, whereas 31% of the contractions was immediately followed by a transient lower esophageal sphincter relaxation with reflux. Summary & Conclusions: Prolonged gastric distention in humans induces gastric contractions which are not inhibited by a meal. These gastric contractions can trigger TLESRs and induce gastroesophageal reflux.

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EFFECT OF INTRADUODENAL AND INTRAVENOUS AMINO ACIDS ON PROXIMAL GASTRIC MOTOR FUNCTION IN MAN.

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Digestion of nutrients is divided in the cephalic, gastric, intestinal and post-absorptive phase. Intravenously administered amino acids increase